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Title of Thesis: Blood Viscosity Responses to Exercise and Conditioning in Women

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Title of Dissertation: Blood Viscosity Responses to Acute Exercise and Aerobic Conditioning in Women

Dale Glen Martin, CPT, VC, USA: Doctor of Philosophy 1983

Dissertation Directed by: Earl W. Ferguson, M.D., Ph.D.
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ABSTRACT

Aerobic capacity is limited by the amount of oxygen delivered to the working muscles and the rate of utilization of oxygen at the tissue level. At a given arterial oxygen content the amount of oxygen delivered is a function of blood flow. Blood flow is in turn dependent upon vascular hindrance and blood viscosity. To assess whether aerobic conditioning might alter oxygen transport through changes in blood viscosity, several components of blood viscosity were measured in healthy women. Forty-seven women (fifteen sedentary women, 14 joggers who ran 5-15 miles per week and 18 marathoners who ran more than 50 miles per week) were evaluated. When evaluated by maximum exercise tolerance on the Bruce protocol, they had clearly different maximal aerobic capacities, 34.1 $\pm$ 5.5, 44.8 $\pm$ 4.4 and 51.0 $\pm$ 5.2 ml·kg-1·min-1, respectively, for the sedentary group, joggers and marathoners.

There were no significant differences in resting whole

blood viscosity, hematocrit, plasma viscosity, erythrocyte sedimentation rate, zeta sedimentation ratio or plasma protein concentration among the three conditioning groups. Immediately following exercise and after recovery all groups demonstrated similar changes in blood viscosity factors. Conditioning levels and aerobic capacities did not correlate with resting, exercise or recovery whole blood viscosity or its components.

Whole blood viscosity increased with exercise in all subjects. The increase was greater than can be attributed to an increase in hematocrit. It appears to be due to a coincident increase in plasma protein concentration. However, the increase in whole blood viscosity after exercise was lower than expected given the observed hemoconcentration. This blunted response is attributable to a non-parallel increase in plasma proteins and hematocrit. Plasma protein concentration and, subsequently, plasma viscosity did not rise to the degree expected. This appears to be due to a disproportionate loss of fibrinogen from the protein pool. These changes were seen in each conditioning group and were independent of conditioning level or aerobic capacity.

In summary, in this cross sectional study of women, increases in whole blood viscosity and plasma viscosity were observed with exercise. However, there were no significant differences in resting viscosity factors or in the responses of these factors to exercise based on the level of physical conditioning.

BLOOD VISCOSITY RESPONSES TO ACUTE EXERCISE AND AEROBIC CONDITIONING IN WOMEN

by

Dale Glen Martin

Dissertation submitted to the faculty of the Department of Physiology Graduate Program of the Uniformed Services University of the Health Sciences in partial fulfillment of the requirements of Doctor of Philosphy 1983

DEDICATION

To my mother, father, Linda, Lucas and Lindsay.

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I thank the entire committee for their support. I appreciate it more than words could describe.

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Introduction

Multiple biochemical, hematological and hemodynamic adjustments occur with aerobic conditioning.[7] These changes account for the improved endurance and performance capacities which characterize physically fit individuals.[64,65,66,131] While aerobic capacity depends upon many variables, the ultimate limiting factors in maximal exercise potential are the rate of transport of oxygen to the working muscle and the rate of utilization of oxygen in the working muscles.[131] The cardiovascular system is the limiting factor in determining blood flow and, therefore, oxygen delivery to the tissues. Blood flow is, in turn, determined by arterial pressure, arteriolar geometry, and blood viscosity.[33,154] With all other factors kept equal, any decrease in viscosity of blood would increase the magnitude of oxygen delivery.[36]

Viscosity of blood varies with the hematocrit, plasma protein concentration, temperature, and red cell deformability.[33,149] Many of these variables change with exercise and may change with physical conditioning.[25,114,151] However, the relative contribution of each is unclear. Most previous studies which have evaluated blood viscosity and its relationship to physical fitness have had vague definitions of fitness or have compared normal populations with patients with disease.[54,55,75,95,116]

Altering blood viscosity factors in various cardiovascular disease processes may improve tissue oxygenation

and, therefore, be beneficial.[5,30,36,37,57,100] Whether blood viscosity factors are significantly altered during aerobic conditioning in a healthy population is unclear. Changes in viscosity with conditioning in women have not been evaluted. This study focuses on a population of healthy women in well-defined fitness categories to characterize blood viscosity responses to exercise, and identify differences which may result from aerobic conditioning.

Physiology of Maximal Exercise

The maximal exhaustive exercise is determined by aerobic capacity, anaerobic processes, and motivation.[8,112] The rate of aerobic energy production is dependant on and measured by the oxygen uptake ($\dot{V}O_2$).[29,85,138] During exhaustive exercise the majority of the energy yield occurs from aerobic combustion of glycogen, glucose and free fatty acids.[85] Anaerobic metabolism occurs when exercise intensity is beyond the capacity of the body to maintain a steady state.[76] At maximal exercise, exhaustion is accompanied by high lactate levels. Lactic acidosis and motivation factors determine an individual's final endpoint for a given exercise test.

Controversy still exists over what limits maximal aerobic capacity.[65,88] The volume of oxygen delivered to the tissue (cardiac output multiplied by arterial oxygen content), as well as the potential of the periphery to use oxygen (mitochondrial oxidative enzymes, capillary density, diffusion distance, etc.) are both thought to limit aerobic capacity.[131] During maximal exercise at sea level in normal

individuals the hemoglobin is fully saturated in the pulmonary capillaries before it leaves the lungs.[164] Only at high altitude or with certain lung diseases will the arterial oxygen content be compromised. Pulmonary function is thus not normally a limiting factor in exercise.

There is a high correlation between maximal oxygen uptake and cardiac output.[64] In maximal exercise, cardiac output may increase more than five fold. The increased cardiac output is a result of increased stroke volume and heart rate. Increased preload due to enhanced venous return coupled with an increased myocardial contractility, results in an increase in the stroke volume by as much as sixty percent with upright exercise. The maximal stroke volume is reached before 50 percent of $\dot{V}O_2$ max is achieved. The remainder of the rise in cardiac output is the result of an increase in the heart rate.[7] The heart rate increases almost linearly with oxygen uptake. Maximal heart rates may be four or more times greater than resting values.

In exercising man the cardiac output is redistriubted to the working muscles by significant alterations in vasomotor tone.[42] Vasodilation of resistance vessels in working muscles, as well as vasoconstriction of splancnic regions, directs arterial blood to sites of greatest oxygen consumption. In the working muscle itself, vasodilation is effected through the release of vasoactive metabolites, increasing blood flow as much as 15-20 times above resting levels.[17,144] At high levels of exercise nearly all capillaries in working

muscle are open and diffusion distance for oxygen from red blod cells to myofibrils decreases. Oxygen unloading from hemoglobin is enhanced by a decreased PO_2 in the tissue and by increased hydrogen ion concentration, PCO_2, and temperature. The latter changes shift the hemoglobin-oxygen dissociation curve to the right and increase oxygen unloading from hemoglobin at the tissue level.[152] The ability to utilize oxygen is determined by the oxidative capacity of the tissues which is dependent on mitochondrial enzymes. During exercise, the increase in temperature also increases enzymatic efficiency of the oxidative processes, which convert oxygen into high energy phosphates for work. The summation of the physiologic changes listed above may increase oxygen consumption in the working muscle sixty fold over resting levels.[17] As the demand for oxygen goes beyond the maximal delivery capability, increasing levels of exercise are sustained through the addition of energy by anaerobic metabolism. The amount of energy made available by this process (creatine phophate and glycolysis) is limited.[85] Without oxygen, the end product of the energy release from glucose is lactate or pyruvate. The depletion of energy substrates and the accumulation of lactate may be the limiting factors for voluntary exercise.[76] The ability of a subject to cope with the discomfort of exercise induced by acidosis then becomes a major determinant of the duration of exercise.

Physiology of Aerobic Conditioning

Aerobic physical conditioning results from regularly re-

peated exercise of a sufficient level to increase the capability of the cardiovascular system and working muscles to support high levels of sustained exercise. The best measure of the level of physical conditioning or physical fitness is the maximal aerobic capacity or maximal oxygen uptake ($\dot{V}O_2$ max expressed in liters O_2/min or ml $^{O2}\cdot kg^{-1}\cdot min^{-1}$).[112]

The improvement of maximal aerobic capacity is directly related to the frequency, intensity and duration of training. For aerobic conditioning to occur, training must be sufficient to elevate the heart rate to 75-80% of maximal for 20-30 minutes for a minimum of three times a week.[4] Since total body mass and fat weight are usually reduced in conditioning programs, while lean body mass may increase slightly, it is often useful to express VO_2 max not only in liters/min and $ml\cdot kg^{-1}\cdot min^{-1}$, but also $ml\cdot kg^{-1}\cdot min^{-1}$ lean body $mass^{-1}$.[4]

Physical conditioning results in a number of cardiovascular, musculoskeletal and metabolic adaptations which enhance delivery and utilization of oxygen resulting in greater endurance and higher maximal aerobic capacity. Cardiovascular adaptations include a larger stroke volume and a decreased heart rate at any given submaximal workload.[64,66,85,131] A significant increase in capillary density in exercising muscles decreases the diffusion distance. Enhanced mitochondrial enzymatic capability for pyruvate and fatty acid oxidation (40% over preconditioning levels) increases the potential for oxygen utilization. As a

result an increase in the arteriovenous (A-V) difference in oxygen content at maximal exercise is often observed after conditioning.[83]

The circulating blood volume also expands with conditioning.[47,117] Increases in total hemoglobin and plasma volume as great as 18% and 30%, respectively, have been reported.[23] Because plasma volume increases exceed gains in red cell mass, a decrease in the hematocrits of endurance athletes often occurs.[27] The expanded plasma volume in endurance athletes allows better dissipation of greater thermal loads generated by exercise, while the hemodilution may decrease blood viscosity.[119]

With long term strenuous activity an increased loss of red blood cells may occur.[61,125] This has been termed "sports anemia." Exercise-induced loss of red cells in normal individuals may result from traumatic destruction of cells from such activities as karate, conga drumming and running on hard surfaces.[91,125,128,148] Increased osmotic fragility of the red cells due to low protein diets or heritable red cell abnormalities or diseases may be significant factors in some cases.[36,130,139] With improved training regimens and improvements in running shoes, exercise induced "sports anemia" is less likely to occur in normal individuals.

Rheologic Principles

The hemodynamics during exercise are dependent upon the rheologic or flow properties of the blood and the vascular

hinderance.[43,108] Poiseuille, in 1840, working with stiff tubes and saline-like fluid, was the first to develop a mathematical formula to describe fundamental rheological principles:

$$Q = \frac{\pi \Delta P r^4}{8 \eta l}$$

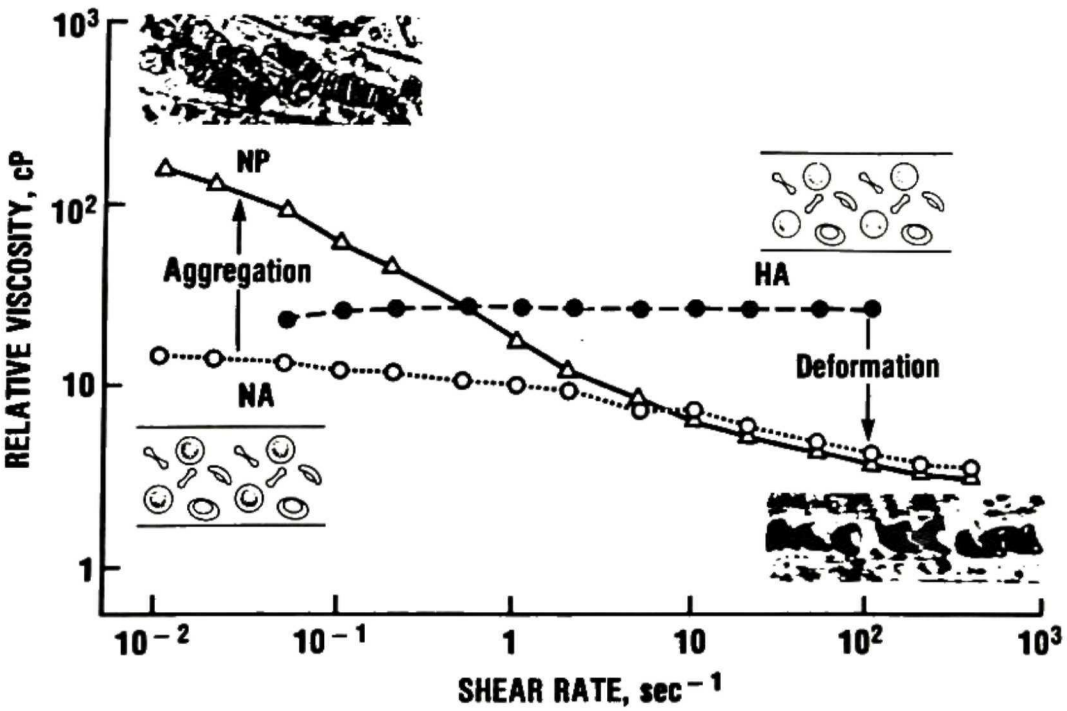
As can be seen from this equation, blood flow (Q) is inversely proportional to the tube (e.g., capillary) length (l) and viscosity (n) and directly proportional to the pressure difference across the tube (i.e., arterial-venous pressure differences) (ΔP) and the radius (r) of the tube raised to the fourth power. $\pi/8$) is the proportionality constant. According to this equation, if length is doubled, flow is halved. In contrast, as the radius is doubled, flow is increased sixteen fold.

Viscosity is a measure of resistance of fluid to flow. It is defined technically as the ratio of shear stress (τ) to shear rate (γ). The shear stress is a measure of force applied in the direction of motion divided by the area of overlap. The shear rate is the velocity of the shearing surface taking into account the thickness of the fluid. The unit of measure of viscosity is the centipoise (cP).

Biological fluids may be defined as Newtonian or non-Newtonian.[108] For Newtonian fluids the viscosity remains constant over a wide range of shear rates. Newtonian fluids include oils, honey, saline, and plasma. However, whole blood is non-Newtonian and the ratio of to is not

constant. Blood viscosity decreases as shear rate increases.[32] The non-Newtonian characteristics of whole blood are due to several factors: 1) red cells tend to agregate when in exposed to low shear rates or undisturbed in plasma, 2) whole blood is in suspension of red cells in a plasma protein mixture and 3) red cells, alone, posses complex viscosity properties.

THE VARIABILITY OF BLOOD VISCOSITY



Modified from: Chein, 1972 and 1975

NP = normal red cells in plasma 1.2 cP
NA = normal red cells in saline albumin 1.2 cP
HA = acetylaldehyde hardened in salien albumin 1.2 cP

The above figure demonstrates the variability of blood

viscosity with shear rate.[32] All three suspensions have an hematocrit of 45% in a suspending media of 1.2 cP. Aggregability of cells caused by bridging of the cells by plasma proteins (especially fibrinogen) markedly increases viscosity at low shear rates. Deformation of red cells (either in albumin (NA) or plasma (NP)) decreases the viscosity of the blood at moderate and high shear rates. Therefore, the non-Newtonian characteristics of whole blood are due to aggregability at low shear rates and deformation at high shear rates. Hardened cells (HA) in suspension cannot aggregate or deform. Therefore, the viscosity remains constant, i.e., Newtonian, at all shear rates.

Normal red cells deform at high shear rates resulting in more efficient flow. As the cells become less deformable the suspension becomes increasingly viscous. Therefore, normal cells in plasma have a much higher viscosity at low shear rates than hardened cells due to increased aggregability, yet have a much lower viscosity at high shear rates due to the ability of the cells to deform.[33]

Whole Blood Viscosity Factors

Blood viscosity is a function of several factors: red cell concentration (hematocrit), plasma viscosity, cell aggregation, and cell deformability.[32,154] These factors are not independent of one another. For example, an increase in hematocrit may also increase aggregability by bringing the cells into closer proximity. A brief discussion of blood viscosity factors follows to explain their significance in

the exercising man.

Hematocrit

Red cell concentration or hematocrit is the single most important determinant of blood viscosity.[10] At a constant plasma viscosity and shear rate, an exponential increase in blood viscosity is observed with elevations in hematocrit.[82] This relationship is lost at very high and low hematocrits.[14,149] At hematocrits below 20% plasma viscosity is the primary determinant of blood viscosity. At hematocrits greater than 50% small increases in hematocrit markedly increase viscosity. Thus, resistance to flow increases at a much greater rate than hematocrit. The tissue PO_2 is a function of the systemic hematocrit and the capillary/systemic hematocrit ratio. Elevation of systemic hematocrit above normal values depresses capillary transport.[98] The tissue PO_2 remains almost constant for hematocrits from 10% to 40%, but significant decreases in tissue PO_2 occur when systemic hematocrit rises above 50%.[98]

Microvascular Hematocrit

The hematocrit in large veins is greater than in smaller vessels. In man the average hematocrit for the entire vasculature is approximately 0.87 of the hematocrit of the large vessels.[82] This difference is due to the low red cell concentration in capillary beds and small bore vessels.[99] In his classical studies, Fahreus showed that the hematocrit of blood flowing through small tubes was less than that in the feeding reservoir.[69] This effect was attributed to the

clustering of red cells in the center of the vessel with plasma streaming along the vessel walls. Red cells in the center move more rapidly than the plasma cuff. As a result, the concentration of red cells in a cross sectional area at any instant is lower than the concentration that passes through that area in a specified time. The effective hematocrit is thus reduced and consequently the blood viscosity is considerably reduced as compared to that in large vessels.[70,153] In the small vessels and capillary beds the hematocrit may be as low as 8-20%.

The decrease in viscosity due to a low microvascular hematocrit is known as the Fahreus-Linquist effect. Recent *in vivo* techniques have confirmed the effect of reduced microvascular hematocrit on viscosity. Measurements of viscosity by *in vitro* and *in vivo* methods compare favorably in blood vessels at physiologic shear rates.[99] Differences in viscosity as determined by *in vitro* versus *in vivo* methods result from inertial losses which occur in the vasculature *in vivo*.[15,96] In the microvasculature, because of the Fahreus-Linquist effect, plasma viscosity has more influence on whole blood viscosity than in the larger vessels.[81]

Plasma Viscosity

The second major determinant of whole blood viscosity is plasma viscosity. Plasma viscosity is primarily dependent on plasma protein concentrations and temperature. Between 27°C and 37°C a linear inverse relationship exists between temperature and plasma viscosity.[123] For every degree increase in

temperature the viscosity decreases by two to three percent.

Plasma viscosity is strongly correlated with plasma protein concentration. Fibrinogen and globulin fractions have the greatest influence and albumin has minimal effects.[35,40] Proteins increase viscosity through perturbations of fluid streamlines. The more asymmetric the molecule, the greater its hydrodynamic effect.[154] Fibrinogen, because of marked axial asymmetry, produces the greatest influence on plasma viscosity. The large globulin proteins also affect plasma viscosity, but crystalloids and smaller more spherical albumin molecules do not.

Aggregability

The third major determinant of whole blood viscosity is red blood cell aggregability. This is the tendency for red cells to interact to form rouleaux or microaggregates of cells. The attraction of red cells for each other is primarily dependent on macromolecular bridging by plasma proteins (primarily fibrinogen).[40] Aggregability is also influenced by extrinsic factors, such as shear stress at the cell surface, cell concentration, and plasma protein concentration.[35,36] Intrinsic properties of red cells, such as affinity for plasma proteins, surface electric charge (zeta potential) and deformability also affect aggregability. During flow, the forces that favor red cell aggregation are counteracted by shear stresses at cell surfaces.[149] In slow flow areas of the circulation, where the shear stress is very low, aggregates of red cells readily form. As shear rates

increase there is a gradual breaking up of aggregates into rouleaux, then total dispersion of the cells.[93] The dispersion of red cells decreases viscosity by reducing perturbations in fluid streamlines.[154]

Affinity of red cells for plasma proteins determines the bridging between cells and is in large part dependent on the surface electric charge of the cell. N-Acetylneuraminic acid residues on the exterior of the bilipid membrane give a net negative charge (the zeta potential) to the red cell.[102] The greater the zeta potential the greater the repulsive forces between cells. As red blood cells age their zeta potential decreases and they aggregate more readily. The concentration of red cells is also a determinant of aggregability since as red cell concentration increases, the closer proximity of individual red cells favors cell-cell interaction.[53]

Red cells must also be flexible for macromolecular bridging to occur and cannot aggregate when hardened by treatment with acetylaldehyde.[32]

Aggregability of cells is difficult to quantify. It may be assessed directy by optical methods, low shear rate viscometry, or erythrocyte sedimentation rates.[56,93] The zeta sedimentation ratio is a relatively recent method which assesses aggregability without having to correct for changes in hematocrit.[24,26,149]

Red Cell Deformability

The last major deteminant of whole blood viscosity is the deformability of the red cell. Deformability is

determined by the interaction of membrane properties, cell geometry, and the internal viscosity of the erythrocyte.[33,106,107,109,132]

The red blood cell membrane is a fluid mosaic of proteins floating in a lipid bilayer. The membrane is quite flexible and the cell behaves as a fluid droplet around which the membrane rotates in a manner described as "tank treading".[74,133] Only under pathologic conditions does the membrane become a significant factor in affecting the deformability of the cell.[134]

The biconcave disc shape of the red cell gives it a large excess of membrane per unit volume of cellular contents. This excess of membrane allows marked deformation of the cell without rupturing the membrane. However, in a number of pathologic states including immune mediated hemolytic disease and sickle cell disease, membrane is lost from the surface of the cell. As the surface area (membrane) to cell volume ratio decreases, the risk of cell rupture with deformation increases markedly.

Internal viscosity of the red cell also influences deformability. It is dependent upon the concentration and character of hemoglobin within the cell, and the metabolic state of the cell.[84,162] Increased hemoglobin concentration within individual cells increases internal viscosity. In addition, when aggregation of hemoglobin molecules occurs, as in sickle cells at low oxygen tensions, red cell internal viscosity increases and the cells are much less deform-

able.[38,134] Red cell ATP content and calcium concentration also influence internal viscosity.[41,150] As red cells age the decrease in ATP content and the increase in calcium concentration increase cell viscosity.

Temporal Changes in Blood Viscosity in Premenopausal Women

Blood viscosity factors in women have been reported to change with age, the menstrual cycle, and oral contraceptives.[53,58,86] One report suggests that higher whole blood viscosity in post-menopausal women (ages 55-80) is due to significantly higher fibrinogen concentrations.[58] This study found no significant variations with age in blood viscosities for women between 15 and 55 years of age or in men between ages 15 and 80 years of age. These blood viscosities were measured at moderate and high shear rates, and, therefore, differences in aggregability due to fibrinogen concentrations would not have been detected.

Cyclic variation in blood viscosity with circadian rhythms, as well as menstrual and seasonal cycles have been reported.[12,46,119,136] Hematocrit, plasma protein concentration and whole blood viscosity cycle daily with highest levels occurring in the early morning followed by gradual decreases throughout the day to minimal values near midnight.

Blood viscosity at low shear rates (0.01 sec^{-1}) may be increased twenty-fold in the last week before onset of menses.[56] Viscosity decreases rapidly during menstruation, levels off in the early follicular stage and then remains stable until the third week.[53] The hematocrit remains rela-

tively stable and there is little change in viscosity at higher shear rates during the menstrual cycle. Increased fibrinogen and globulin concentrations which increase aggregability of red cells at low shear rates are probably responsible for the major rheological alterations that occur during the menstrual cycle.[56]

Oral contraceptives have been reported to decrease deformability of red blood cells and increase whole blood viscosity.[6,118] Four male volunteers taking oral contraceptive medication also developed increased filtration times suggesting decreased deformability of red cells. Decreased filtration of red cells demonstrated by Oski was reversed after women discontinued use of oral contraceptives.[118] Dintenfass suggested that much of the increase in viscosity was due to an increase in internal viscosity of the red cell.[53]

As an adaptation to heat stress, plasma volume increases and hematocrit decreases in individuals exposed to the heat during the summer months. Therefore, seasonal variations may result in higher viscosities in the winter and lower viscosities during the summer.[12]

Viscosity and Exercise

Few studies have examined whole blood viscosity with exercise. The results of this limited number of studies suggest increases in whole blood viscosity due to an increase in hematocrit. Since plasma water is lost without an equal loss in plasma proteins, increases in plasma viscosity, as

well as increased red cell aggregability, should increase whole blood viscosity at any given red cell concentration. Increases in hydrogen ion concentration with exercise may alter the deformability of the red cell and further increase whole blood viscosity with exercise. Controlled studies of the effect of conditioning on whole blood viscosity in a healthy population are not available.

Hemoconcentration with Exercise

As discussed above, the concentration of red cells as assessed by the packed cell volume (hematocrit) is the single most important determinant of whole blood viscosity. With short term maximal exercise in humans the hematocrit may increase by 4-10%.[48,157,158]

The hemoconcentration produced by exercise is due to transcapillary shifts which result from increased filtration pressures and increased osmolality of tissues. In man, since the total red cell mass does not change acutely with exercise, any increase in hematocrit reflects a decrease in plasma volume.[89,115] This is in contrast to the dog and horse where marked hemoconcentration, as well as an increase in blood volume, occurs with exercise because of the injection of red cells into the circulation by contraction of the spleen.[104,121,122] The loss of plasma volume from intravascular spaces with exercise in man is thus closely correlated with hematocrit changes and varies with the duration, intensity, and method of exercise.[101,111,136,155,165] With maximal upright treadmill exercise, for example, plasma water

loss varies from 10 to 20%.[48,114]

During moderate to heavy exercise lasting 20 minutes the greatest percentage loss of plasma water occurs in the first six minutes.[111] Plasma water shifts resolve quickly after exercise and hematocrit generally returns to control values between 20 minutes and one hour after exercise.[111]

Plasma protein concentrations are inversely related to plasma water content. The degree of change of plasma protein concentration with exercise is directly related to the degree of acute plasma water movement from the intravascular space. In the past, changes in plasma protein concentration have been used to calculate plasma volume loss with exercise.[2,51] However, several investigators have now demonstrated movement of plasma proteins into and out of the vascular space with exercise.[48,137,155] This loss of plasma proteins varies with the duration, intensity and method of exercise.[155] Almost all proteins remain within the intravascular space with moderate exercise. However, with maximal treadmill exercise, leakage of up to 5.0% of the total protein content may occur.[157,158] Not all investigators have found such protein movements. Senay reported significant losses of plasma proteins with cycle exercise, but not with treadmill exercise.[155]

Optimal Hematocrit

The hemoconcentration of exercise augments oxygen carrying capacity. However, the resultant increase in viscosity reduces blood flow.[32] At very high hematocrits in-

creasing the red cell concentration will not enhance oxygen delivery because it decreases flow.[98] An optimal hematocrit for the transport of the maximal amount of hemoglobin per unit time has been determined *in vitro*.[146] This calculated value for the optimal hematocrit for maximal oxygen delivery closely matches the observed, resting hematocrit for several species, including man. These results suggest that the assumptions made during the *in vitro* simulations, including the impact of viscosity on blood flow are correct.

The optimal hematocrit for oxygen delivery increases as the shear stress increases.[154] With exercise the mean arterial pressure rises, circulation time decreases, and greater shear stresses occur in the circulatory tree. Hemoconcentration thus serves to more closely approximate the optimal hematocrit for the conditions in the vascular tree that occur with exercise. The resulting maximal oxygen transport is enhanced, perhaps contributing to improved aerobic capacity.

Hematocrit in Microvasculature with Exercise

During exercise, blood flow to striated muscle beds is increased. Klitzman found that (in an isolated *in vivo* capillary preparation) moderate stimulation of skeletal muscle markedly increased red blood cell velocity through these vascular beds while almost doubling the hematocrit from 10.4 to 18.7 percent.[92] When these beds were perfused with adenosine to maximally dilate the vessels the hematocrit approached 40 percent.[92] The oxygen supply to tissues is

determined by the rate of flow of red blood cells, not just the hematocrit. Therefore, equal amounts of oxygen may be delivered by a high hematocrit at a low velocity of flow or by a low hematocrit at a high velocity of flow. With exercise, increased flow and the increased red cell concentration both augment oxygen delivery at the capillary level.[92] Red cell concentration still remains low enough (less than 20 percent), however, that the plasma viscosity is a major determinant of overall viscosity of the blood.[99]

Plasma Viscosity with Exercise

During exercise, concentration of plasma proteins increases plasma viscosity.[16,95] The increase in plasma viscosity has been reported to be independent of conditioning level. Globulin and albumin concentrations were observed to increase while fibrinogen concentrations remained unchanged from pre-exercise values.[73,95] Letcher concluded that fibrinogen concentration remained stable because of increased fibrinogenolysis with exercise. Others have concluded that significant fibrinogenolysis does not occur with exercise.[73,82] Increased deposition of fibrinogen as fibrin within the vasculature may explain the failure of fibrinogen concentrations to increase as greatly as globulins with plasma water loss.[72] Minimal changes in fibrinogen concentration with exercise blunt the rise in plasma viscosity and it rises much less than would be expected from the degree of hemoconcentration.[95]

Aggregability with Exercise

Very little is known about the effects of exercise on red cell aggregability. In *in vitro* methods (erytrhocyte sedimentation rates and zeta sedimentation ratios) one would expect increase in aggregability measurements because of increased red cell and plasma protein concentrations. As hematocrit increases with exercise, individual cells have less distance between them, thus, bridging of red cells by plasma protein (which are also hemoconcentrated) may occur more easily. However, *in vivo*, aggregability of red cells may decrease due to 1) decreased circulation time which would place cells in low shear rate compartments of the circulation for shorter period of time, and 2) shifts of blood volume from venous capacitance vessels into arterial circulation and capillary beds. Here, shear rates are higher and aggregability may play a lesser role.

Red Cell Deformability with Exercise

Exercise may affect the geometry and internal viscosity of the red cell.[20,37] With treadmill exercise, red blood cells have been variously reported to shrink, remain unchanged or swell.[48,156,157,160] Changes in the erythrocyte size and shape are a function of the pH and osmolality of the blood. The intensity of the exercise is the primary determinant of these variables.[157] *In vitro* the red cell behaves as an almost perfect osmometer.[49] In contrast, *in vivo* the red cell is remarkably resistant to increases in osmolality.[157] Changes in pH and osmolality may cause changes in the red cell surface area to volume ratio and affect whole

blood viscosity through altered deformability of the red cells.[32]

In prolonged exercise (2 hours) at 60-75% VO_2 max a 5.5% decrease in MCV was reported by Costill, and was correlated with the degree of increased osmolality.[48] Studies with shorter, more strenuous exercise have reported red cells to be much more resistant to volume changes. In two studies a mean increase of 6.0 and 8.3 percent in plasma oncotic presssure, which would have produced a 4 and 6% decrease respectively in MCV in vitro produced no change in vivo.[156,160] It has recently been shown that with maximal treadmill exercise, erythrocyte swelling may occur when the blood pH is below 7.10 in spite of marked rises in plasma osmolality.[157] The effect upon the red blood cell of marked acidosis of heavy exercise may thus offset the effect of increased osmolality. Acidosis will augment the shift of hydrogen and chloride ions into erythrocytes to increase intracellular osmolarity, counteract increased plasma osmolarity, and minimize movement of water into or out of red cells.[156]

In a recent study, filterability of red cells was reduced the same degree after exercise in coronary artery disease patients and normal subjects.[75] However, this study also reported no change in plasma viscosity after exercise, which is contrary to other published reports.[95]

Conditioning Level and Whole Blood Viscosity

As stated earlier, multiple physiological adaptations

occur during aerobic conditioning to further increase oxygen delivery to the muscle tissue with exercise.[7,131] The effect of increasing fitness levels on factors affecting blood viscosity is ill-defined. Previous studies which have examined blood viscosity factors with fitness levels have been very limited in scope have had significant defects in design.[29,54,55] Several studies by Dintenfass and coworkers evaluated fitness level and blood viscosity factors.[54,55] The fitness level was obtained by an arbitrary formula (the square root of the total cycle ergometer work load minus 1.41 x height in centimeters divided by 0.74 multiplied by the age in years plus 113). Twenty subjects with coronary artery disease, twelve subjects with "low energy syndrome", four subjects with obstructive airway disease, and fifteen normals were evaluated. Increases in whole blood viscosity, plasma viscosity, red cell aggregability and fibrinogen concentration were observed in the less fit individuals.

It is well-established many types of cardiovascular diseases are associated with multiple rheological perturbations.[18,36,145] Improvement of blood viscosity factors is associated with improved clinical and prognostic evaluation.[5,30,37,68] Studies such as these help define normal versus abnormal patterns rather than the effect of conditioning or fitness level on blood viscosity patterns.

A recent abstract reported decreases in blood viscosity after an eight week conditioning program in nine men.[28] The decrease was attributed to a decrease in hematocrit.[28] How-

ever, aerobic capacity was not measured before or after conditioning to quantify and document a training effect.

Conditioning and Hematocrit

As stated earlier blood volume expands with endurance training.[23,27,117] Many investigators have reported increases in plasma volume greater than red cell mass with a resultant decrease in the resting hematocrit.[27,151] Other studies have reported no significant difference in the resting hematocrit of athletes versus sedentary subjects.[9] Whether or not a decrease in hematocrit is beneficial for increased aerobic capacity is unknown. One study reported a strong correlation between maximal aerobic capacity and total body hemoglobin but not hematocrit.[20]

Conditioning and Plasma Viscosity

To date only one study in the literature addresses the effect of endurance training on plasma viscosity.[95] Letcher observed a significantly lower resting plasma viscosity in runners (1.20 $\pm$ 0.04 cP) than in non-runners (1.25 $\pm$ 0.03 cP). The groups were small (11 men, and one woman in the running group and 12 men and 1 woman in the non-running group) and the differences between the measured plasma viscosities were small (less than 5%). The study concluded that these differences were due to a significantly lower fibrinogen concentration in the runners compared with the non-runners (272 $\pm$ 42 mg/dl versus 307 $\pm$ 45 mg/dl respectively). Hemodilution due to an increased plasma volume with endurance training was suggested as a possible explanation. However,

hematocrit and plasma albumin concentrations were similar in the two groups of subjects before exercise which suggests a specific effect upon fibrinogen levels.

Other studies of plasma protein concentrations with varying fitness levels have revealed similar findings. Since plasma protein concentrations strongly correlate with plasma viscosity, it is unlikely that differences in plasma viscosity would have been observed in these studies. It is known that several diseases including hypertension and many cardiovascular disorders, result in significant elevations in plasma viscosity.[37,94] However, little is known about the effects of conditioning on plasma viscosity.

Conditioning and Aggregability of Red Cells

Very limited data are available on aggregability of red cells at various fitness levels. In a rheology text Dintenfass reports that average values for aggregability (measured by erythrocyte sedimentation rates) are much lower for athletes than for a "normal" hospital population.[53] However, the data for the "athletes" was an average from nine individuals cited from unpublished data with no information on the level of training, ages, etc. Furthermore, acute illness is often associated with an increase in fibrinogen as one of a number of acute phase reactants. Thus, even a "normal" hospital population would be expected to have elevations in aggregability independent of conditioning.

The lower resting values for fibrinogen concentration in athletes reported by Letcher should also result in a de-

creased aggregability. However, fibrinogen concentrations did not vary with conditining levels in several other studies.[72,73,105]

In addition, two reports suggest an increased erythrocyte turnover rate in endurance training.[126,129] This should result in a younger red cell population with greater repulsion forces and decreased aggregability.

Conditioning and Red Cell Deformability

Even less is known about the effects of conditioning on red blood cell deformability. Marked decreases in red cell filterablity have been noted in patients with cardiovascular disease and sickle cell disease as well as in smokers and diabetics.[37,113,127,161] However, normal individuals with different fitness level have not been studied.

Specific Aims

As outlined above, changes in blood viscosity could favorably change blood flow and, thus, oxygen delivery to the working muscle. Because very little is known about blood viscosity alterations with maximal exercise or the effect of endurance training on various blood viscosity factors, especially in women, blood viscosity factors were compared before and after maximal exercise in three healthy, well-matched groups of women who differed in fitness level.

The specific aims of the present study were:

1. To evaluate the effects of acute maximal exercise on factors affecting whole blood viscosity in women.

2. To evaluate the effects of aerobic conditioning on

the various determinants of whole blood viscosity in women.

Materials and Methods

Subject Evaluation

Forty-seven healthy, non-smoking, premenopausal adult women were evaluated. Fifteen were on no regular exercise program and were categorized as sedentary. Fourteen were running 5-15 miles per week and were considered moderately conditioned ("joggers"). Eighteen who ran more than fifty miles per week were classified as highly conditioned ("marathoners"). The three groups were matched as closely as possible for age, and body habitus. Attempts were made to find lesser conditioned subjects who were lean. All subjects completed a medical history questionnaire (Appendix 2).

All subjects were free of detectable cardiovascular diseases as determined by a medical examination which included a twelve-lead electrocardiogram. Potential subjects with a clinical history or other evidence of medical problems which could limit a maximal exercise performance were excluded from the study. The subjects were free from any medication for at least one week prior to the study. Subjects who had taken aspirin in the previous ten days or oral contraceptives in the previous three months were excluded from the study. All sedentary subjects and joggers and ten of the marathoners were eumenorrheic. Of the other eight marathoners, two were oligomenorrheic and six amenorrheic. No pathological basis for the irregular or absent menses was detected in these eight runners and their amenorrhea/oligo-

menorrhea was presumed to be exercise-induced.

Body Fat Determination

Whole body density was determined by skinfold measurements according to Pollack and by hydrostratic weighing.[124] Skinfold thickness measurements were taken at the chest, scapula, triceps, abdomen, suprailiac, anterior thigh, and axillary regions. A fold of skin and subcutaneous tissue was separated away from the underlying muscle and the thickness measured and recorded to the nearest 0.1 mm using Holtain skinfold calipers with a constant pressure of 10 gm/mm^2. The equation used to determine body density was the sum of seven skinfolds:[87]

a) Sum 7 = Chest + Abdomen + Axilla + Subscapular + Suprailiac + Triceps + Thigh (Equation 1).

b) Body Density = D = 1.0970 - 4.6971x10 -4x (sum 7) + 5.6x10 -7x (sum 7) - 1.2828x10 -4x(age). (Equation 2).

Hydrostatic weighing was performed in a four foot deep by six foot in diameter tank using a chair suspended from a Chatillon 15 kg scale. Subjects forcefully exhaled as much air as possible and the three heaviest of eight readings were averaged to obtain the underwater weight. Residual volumes were estimated from a standardized chart.[11] The body density was calculated by the following formula:

$$D = \frac{Wa}{\frac{(Wa - Ww)}{Tc}} - RV \qquad \text{(Equation 3)}$$

D = Density
Wa = Weight in air in kg
Ww = Weight totally submerged in water in kg
Tc = Correction factor for temperature of water
RV = Estimated residual volume in liters

Percent body fat was then calculated according to the formula of Siri:[141]

$$\%Fat = 495/D - 450 \qquad \text{(Equation 4)}$$

Lean body mass was calculated from body weight and total body fat according to the formula below.

$$WTlean = WT - (\%Fb \times Wt) \qquad \text{(Equation 5)}$$

WTlean = lean body mass in kg

WT = body weight in kg

%Fb = percent body fat

Exercise Protocol

Subjects rested for 15-20 minutes in a reclining chair before resting measurements and the first blood sample were obtained. Subjects then exercised on a treadmill according to the multistaged Bruce protocol.[103] On this protocol treadmill speed and grade increased in three minute stages. Stage I was 1.7 m.p.h. at a 10% grade with progressive increases to Stage VI which was 5.5 m.p.h. at a 20% grade.

Electrocardiograms were monitored on each subject before, during, and after exercise with a 12-lead Quinton Instrument Model 633. Pre-gelled electrodes were placed on dry skin previously cleaned with alcohol and painted with benzoin. A Beckman Metabolic Measurement Cart (MMC) was used to analyze and record oxygen consumption, respiratory quotient and other cardiorespiratory variables every 30-60 sec

at rest, during exercise and during recovery. The MMC was calibrated before and after each study and only changes in calibration of less than one percent were considered acceptable.[13]

All subjects were encouraged to exercise on the treadmill to exhaustion. Objective criteria for maximal effort included more than a three fold increase in blood lactate concentrations, a plateau in heart rate or oxygen consumption and a respiratory quotient of greater than 1.0. The data on subjects who failed to exert themselves to a maximal degree as defined by these criteria, were excluded from the analysis.

Blood Sampling

Blood samples were drawn from the antecubital vein at rest, immediately after exercise and after one hour of recovery, using a two syringe technique. Micro-hematocrits were obtained using a IEC model MC centrifuge. At least three measurements were taken for each sample and recorded to the nearest 0.15% on a Damon/IEC microcapillary reader. The multiple readings were averaged and recorded to the nearest 0.1%. Hematocrits were not corrected for plasma trapping. Red blood cell counts were determined in a Coulter counter. Hemoglobin concentration was determined to the nearest 0.1% in a Coulter Hemoglobinometer by the cyanomethemoglobin method. Red blood cell indices were calculated from the blood cell counts, hematocrits (corrected for plasma trapping) and hemoglobin concentrations using the calculations

listed below:[21,39]

$$MCV = \frac{(HCT \times 10) \times 0.96}{RBC} \qquad \text{(Equation 6)}$$

$$MCHC = \frac{100 \times Hb}{HCT \times 0.96} \qquad \text{(Equation 7)}$$

MCV = mean corpuscular volume in femtoliters = 10^{-15} liters
MCHC = mean corpuscular hemoglobin concentration
HCT = microhematocrit in percent
Hb = hemoglobin in gm/dl

Plasma Protein Concentrations

Total plasma proteins were measured with a hand-held American Optical AO TS Goldberg Meter. Fifty microliters of plasma were placed on the cleaned surface of the refractometer and read to the nearest 0.1 gm/dl. The accuracy of total plasma proteins by refractometry is $\pm$ 0.1 gm%.[3] Total serum protein, albumin, and globulin were measured using a Centrifichem System 500 and standard procedures.

Fibrinogen Concentrations

Fibrinogen concentration was assayed by a clot weight method. Nine ml of blood was anticoagulated with 1.0 ml 0.06 M sodium citrate and 0.04 M citric acid, pH 7.4. Plasma was separated by centrifugation (12,500 g for 20 min at 4°C), placed in a separate polystyrene tube, double sealed with parafilm, frozen and stored at -70°C until analyzed. Ten NIH units of thrombin in 1.0 ml of 0.025% calcium chloride was added to 1.0 ml of plasma, a wooden applicator stick was placed in the solution and the resultant clot was incubated for 30 min in a 37°C water bath. The fibrin clot was wound tightly onto the wooden stick, separated from the serum and

placed in 2.0 ml of deionized water. After 30 min at 37°C the fibrin clot was removed from the stick, blotted on filter paper and placed in 2 cc of acetone for 10 min. The clot was then removed, placed in a glass test tube in a drying oven at 37°C for twenty hours. The clot was weighed with a Mettler H54 AR scale to the nearest 0.2 mg. The weight of the fibrin clot was calculated as follows:

$$C_w = \frac{\text{Clot (mg)} \times 100}{1.0 \text{ ml Plasma}}$$

Fibrinogen concentration was calculated using the following formula:

$$Fc = Cw \quad \frac{1.11 - \frac{HCT}{100}}{1 - \frac{HCT}{100}}$$

Fc = fibrinogen concentration in mg/dl
Cw = measured clot weight
HCT = measured hematocrit

The formula corrected for hemodilution of the citrate added during anticoagulation.

Lactate and Pyruvate Concentrations

Blood lactates and pyruvates were determined by standard methods (Sigma Technical Bulletins 826-UV and 726-UV, respectively).[140] One ml of whole blood was placed into one ml of cold eight percent perchloric acid, agitated vigorously, and then placed on ice for analysis within four hours. Lactic acid concentration was determined as the amount of NAD generated from the conversion of lactate to pyruvate. NAD was measured by changes in absorbance at 340 nm. Pyruvate was determined by NADH generated from conversion of pyruvate

to lactate by LDH. NADH was measured by changes in absorbance at 340 nm.

Calculation of Plasma Volume Change with Exercise

Percent plasma volume change with exercise was calculated using two methods. One method uses only changes in hematocrit[158] and the other uses changes in both hematocrit and hemoglobin concentration.[51,147] Microhematocrits were multiplied by the factor, (0.96 x 0.91) to correct for trapped plasma and to convert to whole body hematocrits:[159]

$$\% \Delta PV1 = \frac{100}{100-HCTc} \times \frac{HCTc-HCTe}{HCTe} \times 100 \quad \text{(Equation 10)}$$

$$\% \Delta PV2 = 100 \left[\frac{Hbc(100-HCTe)}{Hbe(100-HCTc)}\right] - 100 \quad \text{(Equation 11)}$$

% ΔPV = change in plasma volume in percent
HCTc = control measured hematocrit (0.96) (0.91)
HCTe = exercise measured hematocrit (0.96) (0.91)
Hbc = control hemoglobin concentration gm/dl
Hbe = exercise hemoglobin concentration gm/dl

Calculations of Plasma Protein Concentration Change and Content Change with Exercise

The percent change in concentrations of plasma proteins, hematocrit and hemoglobin were calculated from pre test values as follows:

$$\%\Delta Cn = \frac{Cc-Ce}{Cc} \quad \text{(Equation 12)}$$

%Δ Cn= Percent change in concentration
Cc = Control concentration
Ce = Exercise concentration

The concentration of a plasma solute is related to the change in plasma volume. The percent change in protein content was calculated by two methods.[79,157] One method

uses changes in hematocrit and the other uses changes in hematocrit and hemoglobin concentration.

$$\%\Delta Co = \frac{Ce(HCTc(100-HCTe))-Cc(HCTe(100-HCTe))}{\frac{Cc(HCTe(100-HCTc))}{100}} \quad \text{(Equation 13)}$$

$$\%\Delta Co = \frac{Ce[Hbc(100-HCTe)]-Cc[Hbe(100-HCTc)]}{\frac{SCc[Hbe(100-HCTc)]}{100}} \quad \text{(Equation 14)}$$

%Δ Co = percent change in protein content
Cc = Control concentration
Ce = Exercise concentration
HCTc = Control hematocrit
HCTe = Exercise hematocrit
Hbc = Control hemoglobin
Hbe = Exercise hemoglobin

Whole Blood Viscosity Measurements

Whole blood viscosity was determined within three hours from the time blood was drawn and anticoagulated with di-sodium ethylenediaminetetraacetate (EDTA) using a Wells-Brookfield viscometer.[163] This cone and plate viscometer allows direct measurements of shear stress and shear rate. Measurements were taken on whole blood at native hematocrit and hematocrit standardized to 45% with autologous plasma. This viscometer is essentially a precise rotating torque-meter. The resistance of the blood to flow is sensed as it rotates over the flat surface (plate). This torque, which can be measured at a variety of rotational speeds, causes a deflection of a needle which is read on a dial. This reading is easily converted to viscosity in centipoise by using the appropriate equations listed below.

For non-Newtonian fluids the shear stress and shear rate were calculated for the cone and plate viscometer.[60]

$$\tau = \frac{T}{2/3\ r^3} \qquad \text{(Equation 15)}$$

$$\gamma = \frac{2\ N}{\frac{60}{\sin\theta}} \qquad \text{(Equation 16)}$$

τ = shear stress (dynes/cm^2)
γ = shear rate (sec^{-1})
r = spindle radius = 2.40 cm
N = instrument speed in RPM (1.5,3,6,12,30,60)
θ = cone angle (0.8^o)
T = percent full scale torque

$$\eta = \frac{\tau \times 100}{\gamma} \qquad \text{(Equation 17)}$$

η = viscosity in centipoise

The viscometer was calibrated as described by the Brookfield Engineering Laboratories operating instructions.[22,163] When properly calibrated the pins on the cone and plate are 0.0005 inches apart. Each day the calibration was checked by viscosity standards of 4.9 centipoise at 37^{o}C.

Five hundred microliters (0.500 ml) of anticoagulated blood were placed into the rhodium cup (plate) which was encased with a constant temperature circulating water bath at 37^{o}C. The cup was gently attached to the ring joining the viscometer. This brought a shallow 0.8^o cone in the viscometer in close proximity to the plate. The viscometer was run at 1.5 RPM for 30-60 sec before the first reading from the dial was taken. Successive readings were taken at 10-15 sec intervals at rotational speeds of 3,6,12,30 and 60 RPM's. The dial readings are reproducible to within one division on the dial at each rotational speed. Therefore, the greatest precision is obtained at the highest rotational speed where

the dial reading is near full scale. The viscometer is accurate to ± 1.0% at full scale readings and reproducible to ± 0.2%. A second 0.500 ml sample was measured in the same way. If the readings were not within two divisions of each other expressed as a number on the dial a third sample was run. The readings were averaged and the absolute viscosity in centipoise was calculated. Between readings, the cone and plate were meticulously cleaned with deionized water and carefully dried. Both surfaces were visually examined to ensure that they were shiny, clean, dry and free from residual blood or plasma before the next sample was run.

Whole blood viscosity was measured on whole blood standardized to 45% hematocrit ± 0.2%. Two 2 ml samples of whole blood were placed in two separate tubes. The amount of plasma to the nearest 0.001 cc needed to add or withdraw from the sample was determined. If the hematocrit of the corrected samples did not fall between 44.8 and 45.2% they were again adjusted with autologous plasma and rechecked. Samples standardized to an hematocrit of 45 ± 0.2% were analyzed in a similar manner as described above for whole blood.

Plasma Viscosity Measurements:

Plasma was obtained by centrifugation of the anticoagulated blood at 5000 RMP for 5 minutes. A 0.500 ml sample was placed in the cup. Three measurements were obtained at 450 sec-1 that agreed within 0.5 dial units. The measurements were averaged and viscosity in centipoise was calculated.[22]

Erythrocyte Sedimentation Rate:

Within 15 minutes of venipuncture whole blood, anticoagulated with EDTA, was placed into Wintrobe tubes. The tubes were filled to the 100 mm mark, and placed upright on a stable surface to minimize the effects of vibration.[56] At one hour, readings were taken to the nearest 0.5 mm at the plasma/red cell interface and recorded as erythrocyte sedimentation rates uncorrected for hematocrit (ESR). Since both the hematocrit and plasma viscosity can affect the sedimentation rates, a chart and methods described by Dintenfass were used to standardize the readings to 45% hematocrit and a viscosity of 1.3 centipoise.[56]

$$ESRc = \frac{(ESR45 \times PV)}{1.3} \qquad \text{(Equation 19)}$$

ESRc = Erythrocyte sedimentation rate in mm corrected to 45% and 1.3 Centipoise

ESR45 = Erythrocyte sedimentation rate in mm corrected to 45% hematocrit

PV = Plasma viscosity in centipoise

Zeta Sedimentation Ratio

Zeta sedimentation ratio (ZSR) is another measurement of aggregability which recently has been used in place of the ESR.[24,26] The results need not be corrected for hematocrit. The ZSR is measured with a zetafuge.[26] The zetafuge applies a precisely controlled centrifugal force across the red cells,[24] which accelerates sedimentation and enhances reproducibility. Tubes (2.0 mm in diameter) are filled with EDTA anticoagulated blood by capillary action. The samples are then placed in the Zetafuge and spun for 45 seconds in a

clockwise direction after which the sample is rotated 180 degrees and spun in the opposite direction. This cycle is then repeated for 3 1/2 minutes. This centrifugal force enhances macromolecular bridging of the cells and rapidly produces aggregates of erythrocytes which sediment at an accelerated rate. The Zetacrit represents the ratio of red cells to plasma volume. This value is then divided by the hematocrit of the sample to obtain the Zeta Sedimentation Ratio.

Statistics

Simple univariate statistics were used in the analysis of these data. Statistically significant changes across time (control, exercise and recovery samples) were determined using the paired Student's t-test. Two tailed unpaired Student's t-tests were used to compare the differences among the subject groups. The differences were considered significant if the P-value was less than 0.05. The values in the tables are generally given in means $\pm$ standard deviations. The values in the graphs are generally displayed as means $\pm$ standard error of the mean.[142]

Correlation coefficients obtained by linear regression were used to determine the degree correlation between two variables. Correlations were used where the underlying hypotheses suggested meaningful relationships might exist. For the entire study group correlations of r=0.288 are significant at the P 0.05 level and r=0.372 are significant at the P 0.01 level. In certain instances multiple

regression was used to rate the variables in order of importance in influencing the independent variable.[142]

Results

General Anthropometric Data

General anthropometric data are given in Table 1. Ages, heights, weights, and lean body mass were similar in the three groups. Percent body fat was distinctly different among the three groups, whether determined by skin fold calipers or underwater weighing. The sedentary subjects had the highest percent body fat, the joggers were intermediate and the marathoners had the lowest percent. The two methods of body fat determination were positively correlated ($r=0.750$) $p<0.01$.

Exercise Performance:

Cardiopulmonary performance data are shown in Table 2. Maximal oxygen uptakes (VO_2 max) were distinctly different among the three conditioning groups. The VO_2 max for sedentary subjects places them in the "average" fitness category according to Nagle.[112] The joggers and marathoners were in the "good" and "excellent" fitness categories, respectively. Times on the treadmill were significantly different among the groups and strongly correlated with the measured VO_2 max ($r = 0.950$) as shown in Figure 1. Resting and 20 min recovery heart rates were inversely correlated with aerobic capacity (VO_2 max), while maximal heart rates were not.

Lactate and Pyruvate:

Resting lactate, pyruvate and lactate/pyruvate ratios were similar among the groups (Table 3). Immediately after

exercise there was, on the average, an eight-fold increase in blood lactate concentration, a two-fold increase in pyruvate levels and a three-fold increase in the lactate to pyruvate ratios for the three groups. The joggers had a higher post exercise lactate concentration than the sedentary or marathoner groups. Exercise lactate, pyruvate and lactate/pyruvate ratios did not correlate with VO_2 max or time on the treadmill.

Hemoconcentration with Exercise

Equations 10 and 11 were used to calculate percent plasma volume loss with exercise (Table 4). Using equation 10 an 11.0% loss was calculated for the entire study group. Equation 11 resulted in a 12.7% plasma volume loss (Figure 2). There were no significant differences among the plasma volume losses in the three groups. The reciprocal rise in total plasma protein concentration was of similar magnitude among the groups and averaged 10.2% (figure 3). The fibrinogen concentration increased an average of only 3.7% (Figure 4). From these data the percent changes in total intravascular plasma protein content and total intravascular fibrinogen content were calculated from equations 13 and 14. From equation 13, the percent change in plasma protein content with exercise was calculated, and averaged -3.9% for all subjects (Figure 5) (Table 5). From equation 14 the percent change in protein content averaged -1.9% for all subjects (Table 5).

The percent change in fibrinogen content decreased by an

average of 9.4% for all subjects using equation 13; and 7.5% for all subjects using equation 14 (Table 5) (Figure 5). Therefore, approximately 7.5 to 9.4% of the intravascular fibrinogen was lost from the intravascular spaces after exercise.

After removing 40-45 ml of whole blood to obtain the control sample, the average total loss of plasma proteins was calcuated to be 1.0-1.3%. Therefore, approximately 0.5-2.7% of total plasma proteins were calculated to be lost from the intravascular spaces due to the maximal exercise stress.

Determinants of Blood Viscosity with Exercise and Conditioning Hematocrit

Control, exercise and recovery hematocrits were similar among the groups (Table 6). With exercise, hematocrits increased 7.2% in sedentary subjects, 9.9% in joggers, and 9.4% in marathoners (Table 7 and Figure 6). The percent increase among the groups were not statistically different. Parallel changes in hemoglobin (6.8% increase), and red blood cell counts (6.8%) were seen with exercise. One hour after exercise hematocrits decreased by 4.1%, 4.9%, and 5.1% in sedentary, jogger and marathoner subjects respectively (Table 8). The total mean decrease of -4.6% in hematocrit is consistent with the calculated red blood cell loss from phlebotomy. Losses of a similar magnitude were seen in hemoglobin concentration and red blood cell counts.

Plasma Viscosity

The plasma protein concentrations and plasma viscosity

before and after exercise are shown in Table 9 and Figures 3 and 7 respectively. At rest, plasma viscosity, total plasma proteins, total serum proteins, globulins, and albumins were similar among the groups. However, the fibrinogen concentration was greater ($p < 0.05$) in the marathoners than in the other two groups (Table 9) (Figure 4). Among all subjects the plasma viscosity before exercise correlated most closely with total plasma protein ($r = 0.804$) (Figure 8). Weaker correlations were observed with total serum protein ($r=0.684$), fibrinogen concentration ($r=0.576$) (Figure 9), globulin concentration ($r=0.459$) and albumin concentration ($r=0.525$). Multiple linear regression analysis, in which plasma viscosity was the dependent variable and fibrinogen, globulin and albumin were independent variables, demonstrated that fibrinogen exerted the greatest effect on plasma viscosity. Globulin and albumin also had a statistically significant yet much smaller influence on the plasma viscosity.

Plasma viscosity = $0.585 + 0.816[F] + 0.076[G] + 0.060[A]$

[F] = fibrinogen concentration

[G] = globulin concentration

[A] = albumin concentration

The three conditoning groups demonstrated similar percentage increases in plasma viscosity, total plasma proteins, and fibrinogen after exercise (Table 7) (Figures 5-7), as well as similar decreases in these variables during recovery (Table 8). The elevation in plasma viscosity and total proteins with exercise was statistically significant p

< 0.01 (Table 9) for all three groups. The fibrinogen concentration after maximal exercise was not significantly increased for any group. However, when the three groups are pooled, an increase ($p<0.05$) in fibrinogen concentration with exercise becomes evident (Table 9). Recovery samples demonstrated significantly decreased plasma viscosity, total plasma proteins, and fibriogen concentrations from resting values (Table 8). A significant decrease (3.7%) in plasma viscosity for the study group was observed at recovery. There was a similar percent decrease in total proteins (5.2%) and fibrinogen concentration (4.6%) observed at recovery. A moderately strong correlation between plasma viscosity and total protein concentration remained upon exercise ($r=0.752$) and recovery ($r=0.782$), as well as a moderately positive correlation with fibrinogen concentration upon exercise ($r=0.553$) and recovery ($r=0.526$) (Figures 8,9).

Whole Blood Viscosity at Native Hematocrit

The whole blood viscosities at native hematocrit (WBVn) measured at six different shear rates before, immediately after, and one hour after exercise are shown in Table 10. Significant increases in WBVn were seen after maximal exercise at all shear rates in all subject groups (Figure 10). One hour after exercise WBVn fell below the control values. Whole blood viscosity decreased with increasing shear rates for all subject groups. With exercise WBVn rose 16 and 19% at shear rates of 11.25 sec-1 and 22.5 sec-1, respectively, while rising 11.8 and 12.6% at 225 sec-1 and 450 sec-1,

respectively. At 450 sec-1 WBVn significantly rose an average of 12.6% in the study group (Table 7). The percent increase in WBVn with exercise was not statistically different among the different subject groups (Figure 12). The increase in WBVn with exercise did not correlate with VO_2 max, time on the treadmill or post exercise lactate concentrations (Figure 12). Hematocrit strongly correlated with WBVn at all but the lowest shear rate (r=0.294 at 11.25 sec-1, r=0.819 at 22.5 sec-1, r=0.853 at 45 sec-1, r=0.860 at 90 sec-1, r=0.785 at 225 sec-1, r=.835 at 450 sec-1) (Figure 13). In multiple linear regression analysis in which WBVn is the dependant variable, most of the variability in WBVn (r^2=0.88) was due to the hematocrit and total plasma protein concentration.

Whole Blood Viscosity Corrected to 45% with Autologous Plasma

When hematocrit was standardized to 45% with autologous plasma (WBV45) control, exercise and recovery blood viscosities were similar among the groups (Table 11). For all subjects pooled a significant increase in WBV45 with exercise was recorded at all shear rates (Figure 14). A positive correlation existed between the increase in WBV45 and the increase in total plasma protein concentration with exercise (r=0.781). The increase in exercise WBV45 varied from 2.8 to 3.9% among the groups (Figure 15). One hour after exercise WBV45 was significantly lower (2.1 to 4.6%) than control samples. Decreases in WBV45 with parallel decreases in plasma viscosity and total plasma proteins were observed with

recovery samples.

Red Cell Aggregation

For all subjects resting ESR and ZSR were only moderately positively correlated (r=0.679). A much stronger correlation was apparent after the ESR was corrected for hematocrit (r=0.856). That correlation was similar to that for the ESR corrected for hematocrit and plasma viscosity (ESRc) (r=0.859) (Fig 16). The control ESRc values for all subjects demonstrated the strongest correlation with fibrinogen concentration (r=0.790) (Figure 17). The control samples also revealed the ZSR to have a positive ocrrelation with the fibrinogen concentration (r=0.697) (Figure 18). Multiple linear regression analysis with ESRc or ZSR the dependant variable and fibrinogen, globulin and albumin concentrations, the dependent variables, demonstrated that fibrinogen was the major determinant of sedimentation rates. Globulins had a significant but minor effect and albumin had no significant effect.

$$ZSR = -23.8 + 89.9[F] + 3.6\ [G]$$

$$ESRc = -22.9 + 80.4[F] + 3.4\ [G]$$

By ESRc and ZSR, no significant differences in aggregability could be demonstrated among the groups before, immediately after, or one hour after exercise (Table 12). A similar and consistent percent change in ESRc and ZSR was observed in the three groups after exercise (Figures 19,20). When the data were pooled for all subjects, ZSR and ESRc were significantly greater with exercise and lower during

recovery.

Red Cell Deformability

The blood viscosity measured in whole blood corrected to 45% with autologous plasma (WBV45) and evaluated at a shear rate of 450 sec^{-1} was similar among the three conditioning groups. The suspending medium (plasma) was also of similar viscosity among the groups. These data are summarized in Table 13. In addition, all red blood cell indices, hemoglobin, red cell count, mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) were similar among the groups at rest (Table 14).

The exercise samples demonstrated increases in hemoglobin concentrations, red blood counts, and MCV and a decrease in the MCHC. The increase in MCV correlated with the decrease in MCHC. The exercise samples WBV45 at 450 sec^{-1} and plasma viscosities were similar among the groups. Recovery samples demonstrated similar decreases in WBV45 at 450 sec^{-1} and plasma viscosity. The MCV and MCHC returned to control values. The decreases in hemoglobin and red cell count with recovery were consistent with the loss of red cell mass from the blood drawing protocol.

TABLE 1

Anthropometric Data

n	Sedentary 15	Joggers 14	Marathoners 18	Significant differences
Age, yr	33.3 ±6.0	33.4 ±5.5	32.1 ±7.3	
Height, cm	165.0 ±11.0	164.0 ±6.2	166.5 ±4.3	
Weight,kg	58.3 ±10.4	55.8 ±4.1	55.1 ±4.9	
Body fat, % (skinfold)	22.7 ±4.3	17.9 ±3.1	15.4 ±3.3	J<S *, M<J * M<S **
Body fat, % (hydrostatic)	24.8 ±5.6	21.4 ±4.0	16.4 ±4.7	J<S *, M<J * M<S **
Lean wt, kg (skinfold)	44.8 ±6.8	45.8 ±3.0	46.5 ±3.5	
Lean wt, kg (hydrostatic)	43.7 ±7.7	43.9 ±4.4	46.0 ±4.2	

* $p < 0.05$; ** $p < 0.01$

TABLE 1. Anthropometric data on test subjects. Values are means ± standard deviation. Asterisks denote significance of difference among the groups.

TABLE 2

	Performance Data			
	Sedentary	Joggers	Marathoners	Significant
n	15	14	18	differences
$\dot{V}O_2$ max, $ml \cdot kg^{-1} \cdot min^{-1}$	34.1 ±5.5	44.8 ±4.4	51.0 ±5.5	J>S *, M>J * M>S **
$\dot{V}O_2$ max, ml/min	1983 ±420	2494 ±283	2810 ±321	J>S *, M>J * M>S **
Treadmill time, min	9.7 ±1.1	12.3 ±0.9	13.9 ±1.1	J>S *, M>J * M>S **
Heart rate, beats/min				
Rest	75 ±16	65 ±10	58 ±7	J<S *, M<J * M<S **
Maximal	185 ±9	183 ±8	181 ±11	
Recovery (20 min)	105 ±13	97 ±7	78 ±9	J<S *, M<J * M<S *

* $p < 0.05$; ** $p < 0.01$

TABLE 2. Summary of performance data. Asterisks denote significance of difference among the groups. $\dot{V}O_2$ max is the maximal aerobic capacity. Values are means ± the standard deviation.

TABLE 3

Lactate and Pyruvate

	Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n=47)
Lactate (mg%):				
Control	7.39 ±1.77	6.91 ±1.32	7.47 ±2.12)	7.28 ±1.78
Exercise	46.86* ±17.13	68.31*† ±15.88	58.49* ±15.37	57.71* ±17.90
Recovery	20.01* ±7.59	21.61* ±7.59	16.95* ±10.11	19.31* ±8.69
Pyruvate mg%				
Control	0.59 ±0.09	0.55 ±0.08	0.58 ±0.12	0.58 ±0.10
Exercise	1.27* ±0.30	1.71* ±0.57	1.67* ±0.48	1.56* ±0.49
Recovery	1.07* ±0.23	1.21* ±0.32	1.02* ±0.30	1.09* ±0.29
L/P Ratio				
Control	12.6 ±2.6	12.9 ±2.8	12.8 ±2.6	12.7 ±2.6
Exercise	36.5* ±8.1	42.3* ±12.4	36.5* ±11.6	38.2* ±11.0
Recovery	18.2* ±4.7	18.6** ±7.2	16.0** ±4.5	17.5* ±5.5

* $p < 0.001$ from control
** $p < 0.05$ from control
† $p < 0.05$ joggers greater than sedentaries and marathoners

Table 3. Lactate and pyruvate concentrations and lactate/pyruvate ratios. Asterisks denotes significance of differences of exercise and recovery samples from control values. The cross denotes significance of difference among groups. The values are means ± the standard deviation.

TABLE 4

Hemoconcentration with Exercise; Percent Change in Plasma Volume and Plasma Constituents with Exercise

% Change	Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n=47)
PLASMA VOLUME BY EQUATION 10	-10.5 ±5.3	-13.9 ±6.4	-13.4 ±5.5	-12.7 ±5.8
BY EQUATION 11	-9.4 ±5.2	-12.1 ±4.1	-11.4 ±6.2	-11.0 ±5.4
HCT	7.2 ±3.9	9.9 ±5.2	9.4 ±4.2	8.9 ±4.5
Hb	5.9 ±4.4	7.4 ±3.2	7.0 ±6.1	6.8 ±4.8
TP	7.9 ±4.6	11.5 ±5.5	11.0 ±7.2	10.2 ±6.0
FIB	2.9 ±7.6	2.9 ±9.2	4.9 ±9.1	3.7 ±8.5

Table 4. Hemoconcentration with exercise. Where PV1 (HCT) = percent change in plasma volume by equation 10; PV2 (HCT,HB) = percent change in plasma volume by equation 11; HCT = % change in hematocrit; Hb = % change in hemoglobin concentration in gm/dl; TP = % change in total protein concentration in gm/dl; FIB = % change in fibrinogen concentration in mg/dl. There were no differences among the groups in the percent change with exercise. The values are means ± the standard deviation.

TABLE 5

Percent Change in Content of Plasma Protein and Fibrinogen with Maximal Exercise

% Change	Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n=47)
PLASMA PROTEIN CONTENT				
BY EQUATION 13	-3.3 ±3.4	-4.0 ±3.5	-3.9 ±3.4	-3.7 ±3.4
BY EQUATION 14	-2.2 ±2.0	-1.8 ±3.3	-1.7 ±4.0	-1.9 ±3.2
FIBRINOGEN CONTENT				
BY EQUATION 13	-7.8 ±6.3	-11.5 ±6.5	-9.1 ±6.9	-9.4 ±6.6
BY EQUATION 14	-6.7 ±6.6	-9.3 ±8.1	-6.8 ±9.4	-7.5 ±8.1

Table 5. Percent change in content of plasma protein and fibrinogen with exercise. Where = percent change in total protein content by equation 13, and percent change in total protein content by equation 14 are recorded. Percent change in fibrinogen content by equation 13 and by equation 14. There were no significant differences among the groups in percent content change with exercise. The values are means ± the standard deviation.

TABLE 6

Hematocrit

	Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n=47)
Control	41.5 ±2.8	40.8 ±2.9	40.8 ±2.2	41.0 ±2.6
Exercise	44.5* ±2.6	44.8* ±2.4	44.6* ±2.6	44.6* ±2.5
Recovery	39.8* ±2.8	38.8* ±3.0	38.7* ±2.5	39.1* ±2.7

*$p < 0.01$ from control

Table 6. Hematocrit change with exercise. Asterisks denote significant differences from control values. Values are means ± the standard deviation.

TABLE 7

Percent Change in Blood
Viscosity Factors After Exercise

	Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n=47)
WBV	10.2 ±6.9	14.3 ±7.3	13.4 ±8.7	12.6 ±7.7
WBV45	3.7 ±2.6	5.0 ±3.1	3.2 ±2.5	3.9 ±2.8
HCT	7.2 ±3.9	9.9 ±5.2	9.4 ±4.2	8.9 ±4.5
PV	5.5 ±3.8	6.5 ±4.4	6.7 ±4.8	6.3 ±4.3
FIB	2.9 ±7.6	2.9 ±9.2	4.9 ±9.1	3.7 ±8.5
TP	7.9 ±4.6	11.5 ±5.5	11.0 ±7.2	10.2 ±6.0
ESRc	21.2 ±38.0	17.0 ±25.5	10.9 ±24.6	16.1 ±29.4
ZSR	4.1 ±4.1	6.0 ±5.3	4.9 ±5.4	5.0 ±4.9

Table 7. Percent change from resting values in blood viscosity factors after exercise. WBV = change in whole blood viscosity as measured at 450 sec^{-1} at 37°C in centipoise (cP). WBV45 = change in whole blood viscosity corrected to 45% hematocrit with autologous plasma as measured at 450 sec^{-1} at 37°C. HCT = change in hematocrit (uncorrected for plasma trapping). PV = % change in plasma viscosity measured at 450 sec^{-1} at 37°C in centipoise (cP). FIB = % change in fibrinogen concentration. TP = % change in total plasma protein concentration. ESRc = % change in erythrocyte sedimentation rate (corrected for hematocrit and plasma viscosity) and ZSR = % change in Zeta sedimentation ratio. There were no significant differences in the percentage increases with exercise among the three study groups. Values are means ± the standard deviation.

TABLE 8

Percent Change from Resting Values in Blood Viscosity Factors after Recovery

	Sedentary	Joggers	Marathoners	All
WBV	-6.2 ±6.8	-6.0 ±5.6	-6.7 ±4.9	-6.0 ±5.6
WBV45	-2.3 ±2.6	-1.6 ±3.0	-2.4 ±2.8	-2.1 ±2.8
HCT	-4.1 ±3.7	-4.9 ±3.1	-5.1 ±4.1	-4.6 ±3.6
PV	-4.4 ±3.9	-3.0 ±3.3	-4.4 ±3.9	-3.7 ±3.7
FIB	-4.4 ±6.4	-4.6 ±5.2	-5.0 ±12.2	-4.6 ±8.7
TP	-5.1 ±4.5	-5.2 ±5.2	-5.3 ±5.0	-5.2 ±4.8
ESRc	-24.2 ±63.9	-26.1 ±42.8	-27.9 ±35.9	-26.9 ±47.8
ZSR	-2.6 ±3.7	-4.4 ±2.0	-5.0 ±4.0	-4.1 ±3.6

Table 8. Percent change from resting values in blood viscosity factors after recovery. WBV = Change in whole blood viscosity as measured at 450 sec^{-1} at 37°C in centipoise (cP). WBV45 = Change in whole blood viscosity corrected to 45% hematocrit with autologous plasma as measured at 450 sec^{-1} at 37°C in centipoise (cP). HCT = Change in hematocrit (uncorrected for plasma trapping). PV = Change in plasma viscosity measured at 450 sec^{-1} at 37°C in centipoise (cP). FIB = Change in fibrinogen concentration. TP = Change in total plasma protein concentration. ESRc = Change in erythrocyte sedimentation rate (corrected for hematocrit and plasma viscosity) mm/hr. ZSR = Change in Zeta sedimentation ratio. There were no significant differences in the percent decrease among the three study groups (recovery versus control). Values are means ± the standard deviation.

TABLE 9

Determinants of Plasma Viscosity

	Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n=47)
CONTROL				
PV,cP	1.35 ±0.06	1.32 ±0.06	1.35 ±0.10	1.34 ±0.08
TP, gm/dl	7.9 ±0.5	7.7 ±0.5	7.6 ±0.8	7.8 ±0.6
FIB, mg/dl	272 ±29	260 ±36	302† ±50	280 ±43
GLOB, gm/dl	2.5 ±0.3	2.3 ±0.3	2.4 ±0.4	2.4 ±0.4
ALB, gm/dl	5.0 ±0.5	5.1 ±0.4	4.9 ±0.4	5.0 ±0.4
EXERCISE				
PV, cP	1.42** ±0.06	1.40** ±0.07	1.44** ±0.10	1.42** ±0.08
TP, gm/dl	8.5** ±0.4	8.6** ±0.6	8.4** ±0.6	8.5** ±0.5
FIB, mg/dl	280 ±29	267 ±37	315† ±43	289* ±42
RECOVERY				
PV, cP	1.29** ±0.07	1.28** ±0.07	1.29** ±0.08	1.29** ±0.07
TP, gm/dl	7.5* ±0.58	7.3** ±0.6	7.2* ±0.68	7.3** ±0.6
FIB, mg/dl	260* ±32	248* ±35	287*† ±39	267** ±39

* $p<0.05$ from control
** $p<0.001$ from control
† $p<0.05$ Marathoners > Sedentary and Joggers

Table 8. Determinants of plasma viscosity. Where PV = plasma viscosity at 450 sec^{-1} at 37°C in centipoise (cP). TP = total plasma protein concentration in gm/dl. FIB = fibrinogen concentration in ng/dl, GLOB = total serum globulin concentration in gm/dl, ALB = total albumin concentration in gms/dl. Asterisks denote significance of differences exercise and recovery samples from control values. The cross denotes significance of difference among the groups. The values are means ± the standard deviation.

Table 10. Whole blood viscosity at native hematocrit. Where C = control sample (pre-exercise), E = Exercise sample (immediately post-exercise), and R = Recovery sample (1 hour post-exercise). Measurements were taken at six different shear rates (11.25, 22.5, 45,90, 225, and 450 sec^{-1}) at 37°C and recorded in centipoise. Asterisks denote significant differences in exercise and recovery samples from control values. There were no differences among the three groups. The values are means $\pm$ the standard deviation.

TABLE 10

Whole Blood Viscosity

Shear Rate		Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n-47)
11.25 sec-1	C	6.35 ±.81	6.05 ±.80	6.07 ±.60	6.15 ±.73
	E	7.23* ±.77	7.34* ±.80	7.40* ±.69	7.33* ±.73
	R	5.66* ±.92	5.68* ±.72	5.68* ±.65	5.77* ±.75
22.5 sec-1	C	5.69 ±.55	5.59 ±.55	5.58 ±.56	5.61 ±.54
	E	6.44* ±.55	6.62* ±.67	6.56* ±.75	6.54* ±.66
	R	5.29* ±.61	5.24* ±.75	5.14* ±.63	5.22* ±.65
45 sec-1	C	4.95 ±.57	4.85 ±.50	4.84 ±.43	4.88 ±.49
	E	5.54* ±.50	5.61* ±.58	5.56* ±.49	5.57* ±.51
	R	4.54* ±.52	4.49* ±.64	4.46* ±.45	4.50* ±.52
90 sec-1	C	4.28 ±.46	4.17 ±.39	4.09 ±.38	4.17 ±.41
	E	4.71* ±.41	4.78* ±.52	4.66* ±.42	4.71* ±.44
	R	3.98* ±.43	3.90* ±.46	3.83* ±.33	3.90* ±.40
225 sec-1	C	3.80 ±.34	3.74 ±.33	3.69 ±.34	3.74 ±.33
	E	4.18* ±.34	4.25* ±.43	4.14* ±.38	4.18* ±.38
	R	3.60* ±.31	3.51* ±.37	3.46* ±.30	3.52* ±.32
450 sec-1	C	3.57 ±.30	3.49 ±.32	3.43 ±.33	3.48 ±.31
	E	3.92* ±.37	3.98* ±.41	3.87* ±.36	3.92* ±.36
	R	3.35* ±.27	3.28* ±.33	3.20* ±.27	3.27* ±.29

*$p<0.01$

Table 11. Whole blood viscosity corrected to 45% hematocrit with autologous plasma. Measurements were taken at six different shear rates,(-11.25, 22.5,45,90, 225, and 450 sec^{-1}) and recorded in centipoise. Asterisks denote significance of difference of exercise and recovery samples from control values. There were no differences among the three groups. The values are means $\pm$ the standard deviation.

TABLE 11

Whole Blood Viscosity Corrected to 45% Hematocrit with Autologous Plasma

Shear Rate		Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n=47)
11.25 sec-1	C	7.25 ±.34	7.26 ±.61	7.34 ±.38	7.29 ±.44
	E	7.53** ±.29	7.49** ±.38	7.63** ±.46	7.56** ±.38
	R	6.90** ±.42	6.93** ±.39	7.10** ±.34	6.97** ±.38
22.5 sec-1	C	6.50 ±.24	6.40 ±.40	6.52 ±.42	6.48 ±.36
	E	6.72** ±.31	6.73** ±.36	6.69* ±.45	6.71** ±.38
	R	6.25** ±.25	6.31 ±.42	6.33** ±.40	6.30** ±.36
45 sec-1	C	5.59 ±.24	5.53 ±.31	5.51 ±.35	5.54 ±.30
	E	5.80** ±.27	5.78** ±.33	5.67* ±.39	5.74** ±.34
	R	5.47* ±.26	5.43 ±.37	5.36* ±.39	5.41** ±.34
90 sec-1	C	4.75 ±.20	4.72 ±.25	4.67 ±.29	4.71 ±.25
	E	4.91** ±.21	4.92** ±.31	4.74 ±.30	4.84** ±.29
	R	4.69 ±.27	4.63 ±.27	4.54 ±.31	4.61** ±.29
225 sec-1	C	4.18 ±.16	4.15 ±.19	4.11 ±.24	4.14 ±.20
	E	4.33** ±.16	4.33** ±.23	4.20** ±.24	4.28** ±.22
	R	4.12 ±.20	4.05 ±.24	3.99** ±.26	4.05** ±.24
450 sec-1	C	3.90 ±.13	3.85 ±.17	3.81 ±.23	3.85 ±.19
	E	4.04** ±.21	4.04** ±.21	3.93** ±.22	4.00** ±.20
	R	3.81** ±.17	3.79 ±.21	3.72** ±.23	3.77** ±.20

*p<0.05
**p<0.01

Table 12. Determinants of red blood cell aggregability. Where ESRc = erythrocyte sedimentation rate standardized to hematocrit and plasma viscosity in mm/hr; ZSR = zeta sedimentation ratio; FIB = fibrinogen concentration in ng/dl; GLOB = total serum globulin concentration in gm/dl; ALB = total albumin concentration in gm/dl. Asterisks denotes significance of differences of exercise and recovery samples from control values. The cross denotes significance of difference among the groups. The values are means $\pm$ the standard deviation.

TABLE 12

Determinants of Red Blood Cell Aggregability

	Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n=47)
CONTROL				
ESRc mm/hr	7.0	6.5	9.3	7.8
	±2.8	±3.2	±6.5	±4.8
ZSR	46.7	45.6	47.5	46.7
	±2.7	±3.4	±4.0	±3.5
HCT, %	41.5	40.8	40.8	41.0
	±2.8	±2.9	±2.2	±2.6
FIB, mg/dl	272	260	302†	280
	±29	±36	±50	±43
GLOB, gm/dl	2.5	2.3	2.4	2.4
	±0.3	±0.3	±0.4	±0.4
ALB, gm/dl	5.0	5.1	4.9	5.0
	±0.5	±0.4	±0.4	±0.4
EXERCISE				
ESRc, mm/hr	8.4	7.5	10.0	8.8*
	±4.7	±3.6	±7.3	±5.6
ZSR	48.6	48.2	49.7	48.9**
	±2.7	±3.1	±2.9	±2.9
HCT, %	44.5**	44.8**	44.6**	44.6**
	±2.6	±2.4	±2.6	±2.5
FIB, mg/dl	280	267	315†	289*
	±29	±37	±43	±42
RECOVERY				
ESRc, mm/hr	5.3	4.8	6.7	5.7**
	±3.3	±2.2	±4.1	±3.4
ZSR	45.5	43.6	45.1	44.8**
	±3.4	±3.2	±3.6	±3.4
HCT, %	39.8**	38.8**	38.7**	39.1**
	±2.8	±3.0	±2.5	±2.7
FIB, mg/dl	260*	249*	287†	267**
	±32	±35	±39	±39

* $p < 0.05$ from control
** $p < 0.01$ from control
† $p < 0.05$ marathoners vs. sedentary, marathoners vs. joggers

TABLE 13

Blood Viscosity Factors Affecting Red Blood Cell Deformability

	Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n=47)
CONTROL				
WBV45, cP	3.90 ±0.13	3.85 ±0.17	3.81 ±0.23	3.85 ±0.19
PV, cP	1.35 ±0.06	1.32 ±0.06	1.35 ±0.10	1.34 ±0.08
MCV, 10^{-15}l	96.3 ±4.5	93.7 ±6.9	98.7 ±8.0	96.2 ±6.6
EXERCISE				
WBV45, cP	4.04** ±0.21	4.04** ±0.21	3.93** ±0.22	4.00** ±0.19
PV, cP	1.42** ±0.06	1.40** ±0.07	1.44** ±0.10	1.42** ±0.08
MCV, 10^{-15}l	97.5 ±3.4	96.0 ±4.2	101.7† ±6.7	98.4** ±5.7
RECOVERY				
WBV45, cP	3.81** ±0.17	3.79 ±0.21	3.72** ±0.23	3.77** ±0.20
PV, cP	1.29** ±0.07	1.28** ±0.07	1.29** ±0.08	1.29** ±0.07
MCV, 10^{-15}l	98.1 ±6.3	94.6 +5.5	99.7 ±7.6	97.5 ±6.5

* $p < 0.05$ from control
** $p < 0.01$ from control
† $p < 0.05$ marathoner vs. joggers

Table 13. Blood viscosity factors affecting red cell deformability. Where WBV45 = whole blood viscosity corrected to 45% with autologous plasma, measured at 450 sec^{-1} in centipoise. PV= plasma viscosity measured at 450 sec^{-1} in centipoise. MCV = mean corpuscular volume in femtoliters (10^{-15}l). Asterisks denote significance of the difference from control. The cross denotes significance of difference among the groups. The values are means ± the standard deviation.

TABLE 14

Red Blood Cell Indices

	Sedentary (n=15)	Joggers (n=14)	Marathoners (n=18)	All (n=47)
CONTROL:				
Hb, gm/dl	14.0 ±1.0	14.0 ±1.1	13.4 ±.9	13.8 ±1.0
RBC, X 10^6	4.32 ±0.34	4.37 ±0.36	4.15 ±0.33	4.27 ±0.35
MCV, X 10^{-15} l	96.3 ±4.5	93.7 ±6.9	98.7 ±8.0	96.2 ±6.6
MCHC, %	35.2 ±0.7	35.8 ±2.4	34.3 ±1.9	35.1 ±1.9
EXERCISE:				
Hb, gm/dl	14.8** ±0.7	15.1** ±1.1	14.3** ±1.1	14.7** ±0.9
RBC, X 10^6	4.56** ±0.31	4.68** ±0.32	4.39** ±0.32	4.53** ±0.33
MCV, X 10^{-15} l	97.5 ±3.4	96.0 ±4.2	101.7†* ±6.7	98.4* ±5.7
MCHC, %	34.8 ±1.1	35.0 ±1.3	33.6†† ±1.1	34.0* ±1.2
RECOVERY:				
Hb, gm/dl	13.5** ±0.84	13.3** ±1.2	12.9** ±0.9	13.2** ±1.0
RBC, X 10^6	4.06** ±0.31	4.11** ±0.34	3.89** ±0.32	4.01** ±0.33
MCV, X 10^{-15} l	98.1 ±6.3	94.6 ±5.5	99.7 ±7.6	97.5 ±6.5
MCHC, %	35.3 ±1.2	35.8 ±1.3	34.7 ±1.1	35.2 ±1.2

* $p < 0.05$ control vs exercise and recovery samples
** $p < 0.001$ control vs exercise and recovery samples
† $p < 0.05$ marathoners vs joggers
†† $p < 0.05$ marathoners vs sedentaries and joggers

Table 14. Red blood cell indices changes with exercise. Where Hb = hemoglobin concentration gm/dl; RBC = red blood count x 10^6, MCV = mean corpuscular volume in femtoliters (10^{-15} l), MCHC = mean corpuscular hemoglobin concentration (%). Asterisks denote the significance of the difference from control values. Crosses denote significance of differences among the groups. The values are means ± the standard deviation.

Figure 1

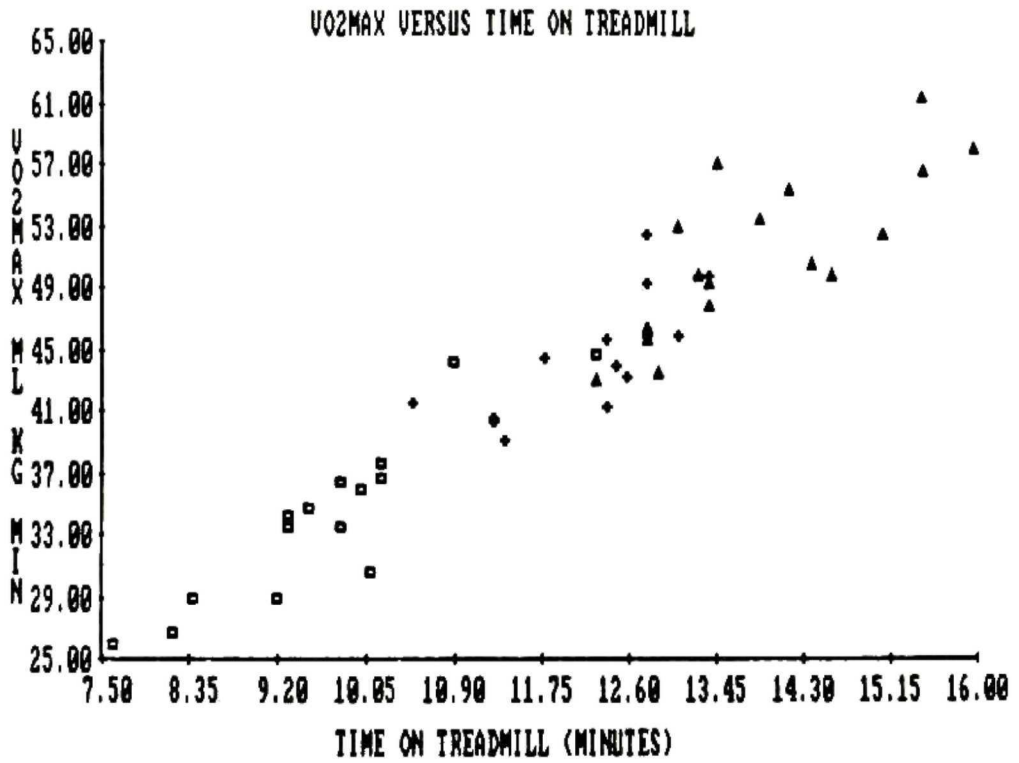


Figure 1. $\dot{V}O_2$ max Versus Time on the Treadmill for All Subjects. Where ◘ are Sedentary, + are joggers and Δ are marathoners. Corelation coefficient between $\dot{V}O_2$ max ($ml \cdot kg^{-1} \cdot min^{-1}$) and time on treadmill (min) was ($r \cong 0.950$).

Figure 2

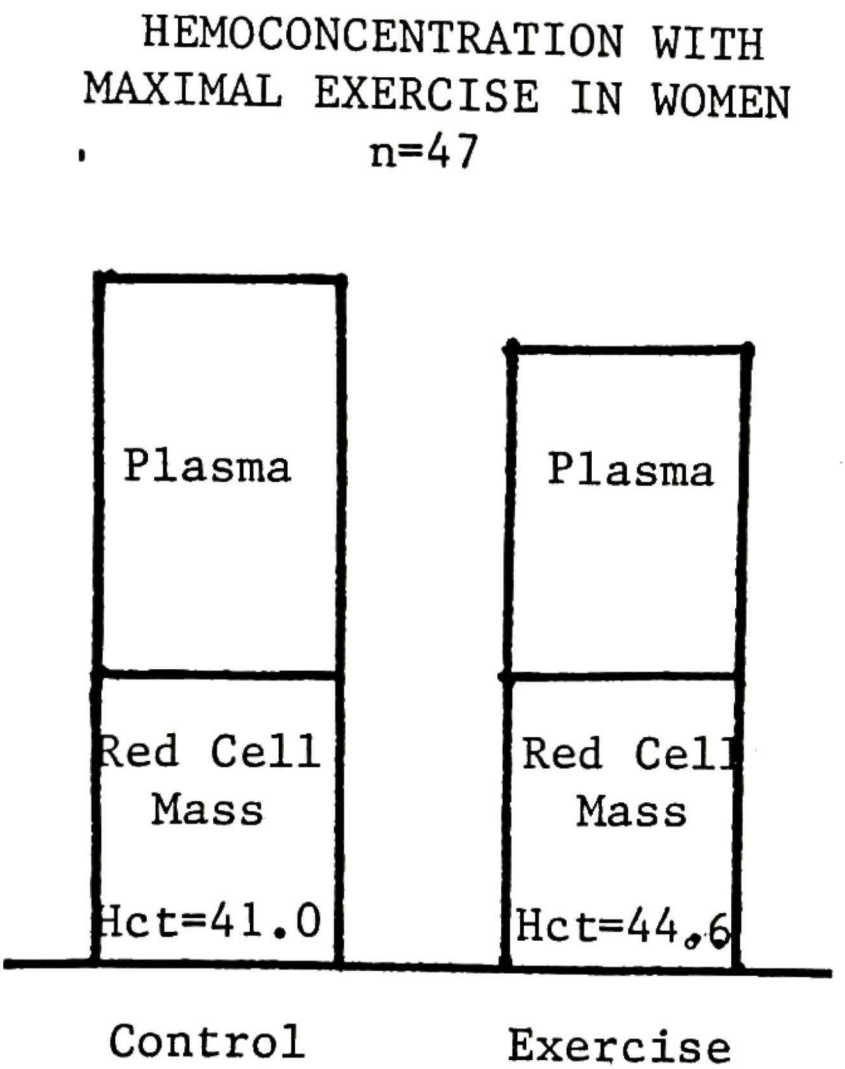


Figure 2. Hemoconcentration with Maximal Exercise in Women. Red blood cell mass remains constant with exercise. The hematocrit rose from 41.0 o 44.6 for the 47 women. The increase in hematocrit is due to loss of plasma volume.

Figure 3

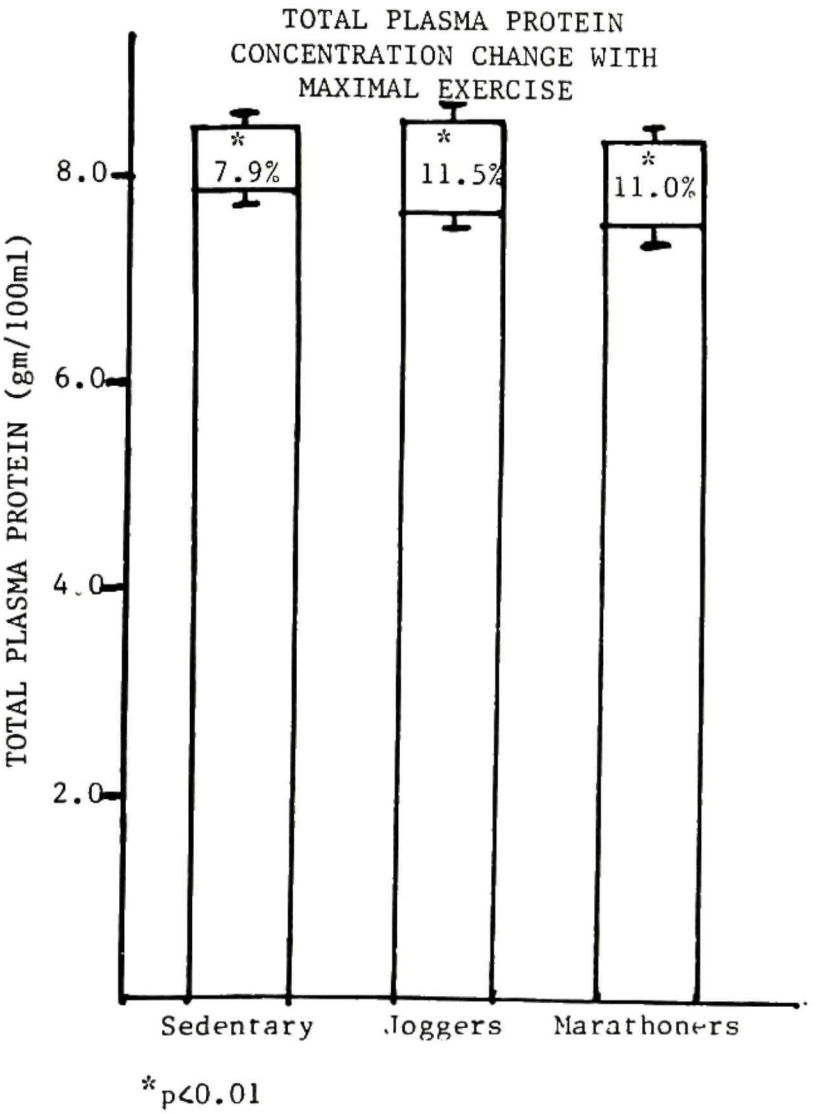


Figure 3. Total Plasma Protein Concentration Change with Maximal Exercise. A significant increase in plasma protein concentration occurred for (15) sedentary subjects, (14) joggers and (18) marathoners. The lower bar represents the control value and the upper bar the exercise value. The brackets represent $\pm$ S.E.M. The asterisks denotes the significance of the difference between the control and exercise values. There were no differences in the control, exercise or percent increase with exercise plasma protein concentrations among the groups.

Figure 4

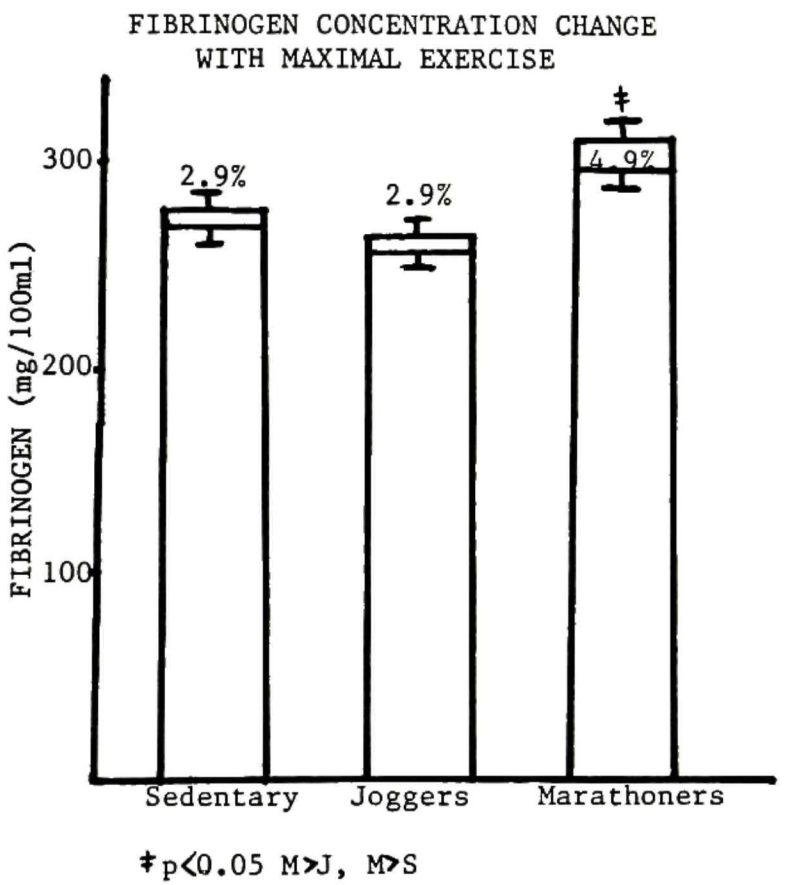


Figure 4. Fibrinogen Concentration Change with Maximal Exercise. Increase in fibrinogen concentrations were not significant for (15) sedentary subjects, (14) joggers, or (18) marathoners. The lower bar represents the control value, the upper bar the exercise value. The brackets represent ± S.E.M. The cross denotes the significance of the difference among the conditioning groups. The control and exercise fibrinogen concentrations was greater in the marathoners when compared to the sedentary and jogger groups.

Figure 5

PLASMA PROTEIN CONTENT AND CONCENTRATION CHANGES WITH MAXIMAL EXERCISE IN WOMEN
n=47

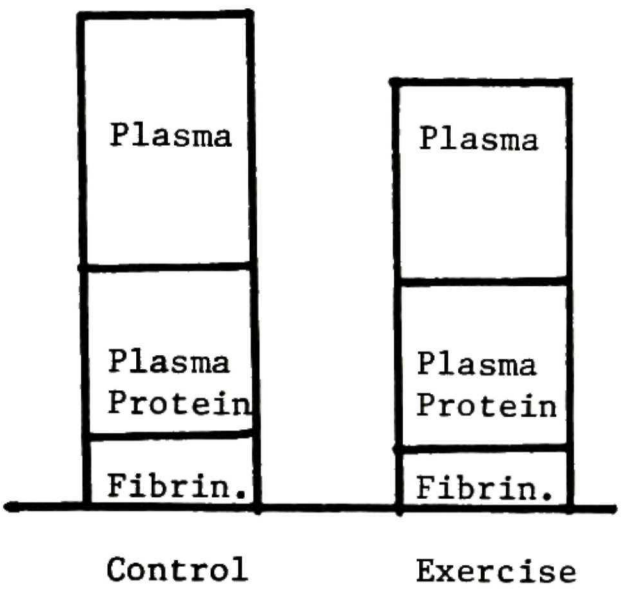


Figure 5. Plasma Protein Content and Concentration Changes with Maximal Exercise. With maximal exercise plasma volume loss occurs (Figure 2). In addition, small amounts of plasma proteins are lost (Table 5). This figure demonstrates a loss of plasma volume, plasma protein content and fibrinogen content (Fibrin). Because much more plasma water is lost than plasma proteins an increase in plasma protein concentration occurs with maximal exercise.

Figure 6

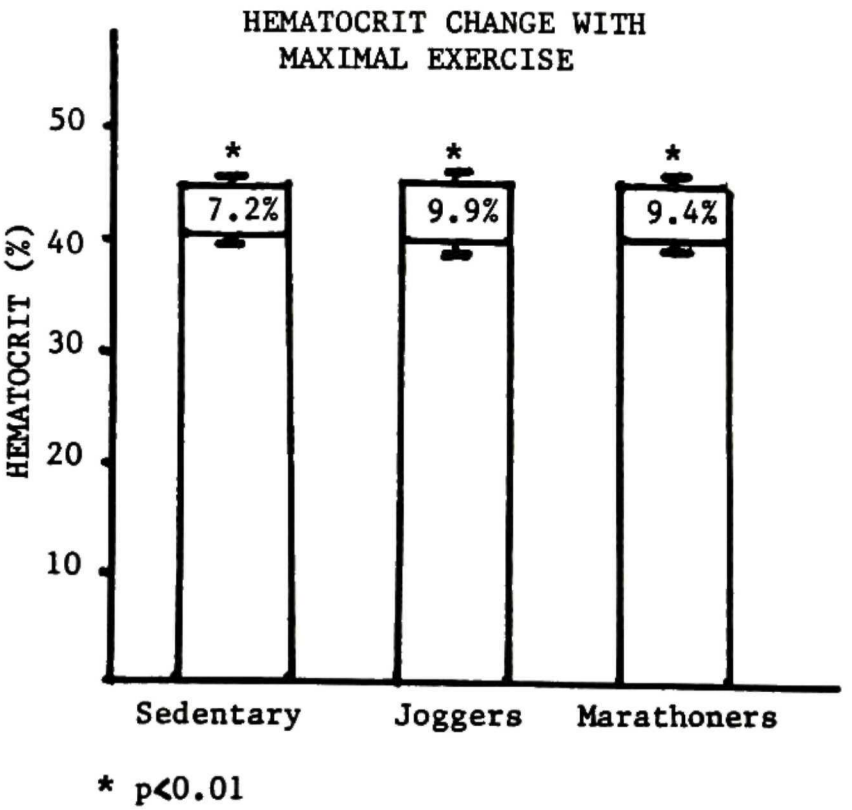


Figure 6. Hematocrit Change with Maximal Exercise. A significant increase in hematocrit occurred for (15) sedentary subjects, (14) joggers and (18) marathoners. The lower bar represents the control values, the upper bar the exercise values. The brackets represent ± S.E.M. The asterisks denote the significance of the difference between the control and exercise values. There was no difference in control, exercise or percent increase in hematocrit with exercise among the groups.

Figure 7

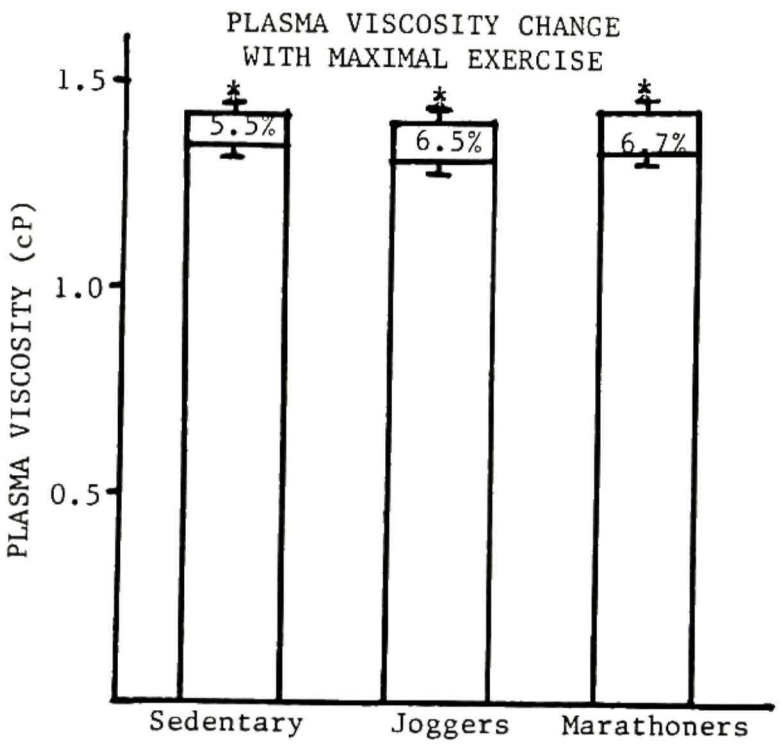


Figure 7. Plasma Viscosity Change with Maximal Exercise. A significant increase in plasma viscosity was observed in the 15 sedentary subjects, 14 joggers and 18 marathoners. The lower bar represents the control value and the upper bar represents the exercise value. The brackets are ± S.E.M. The asterisks denote the significance of the difference between control and exercise values. There were no differences in control, exercise, or percent increase in plasma viscosity with exercise among the three groups.

Figure 8. Plasma Viscosity vs Plasma Protein Concentration. This scatterplot demonstrates a positive correlation between plasma viscosity and plasma protein concentration of control ($r=0.804$), exercise ($r=0.752$) and for recovery ($r=0.782$) samples for the 47 women in the study group. All correlations were significant at teh $p < 0.01$ level.

Figure 8

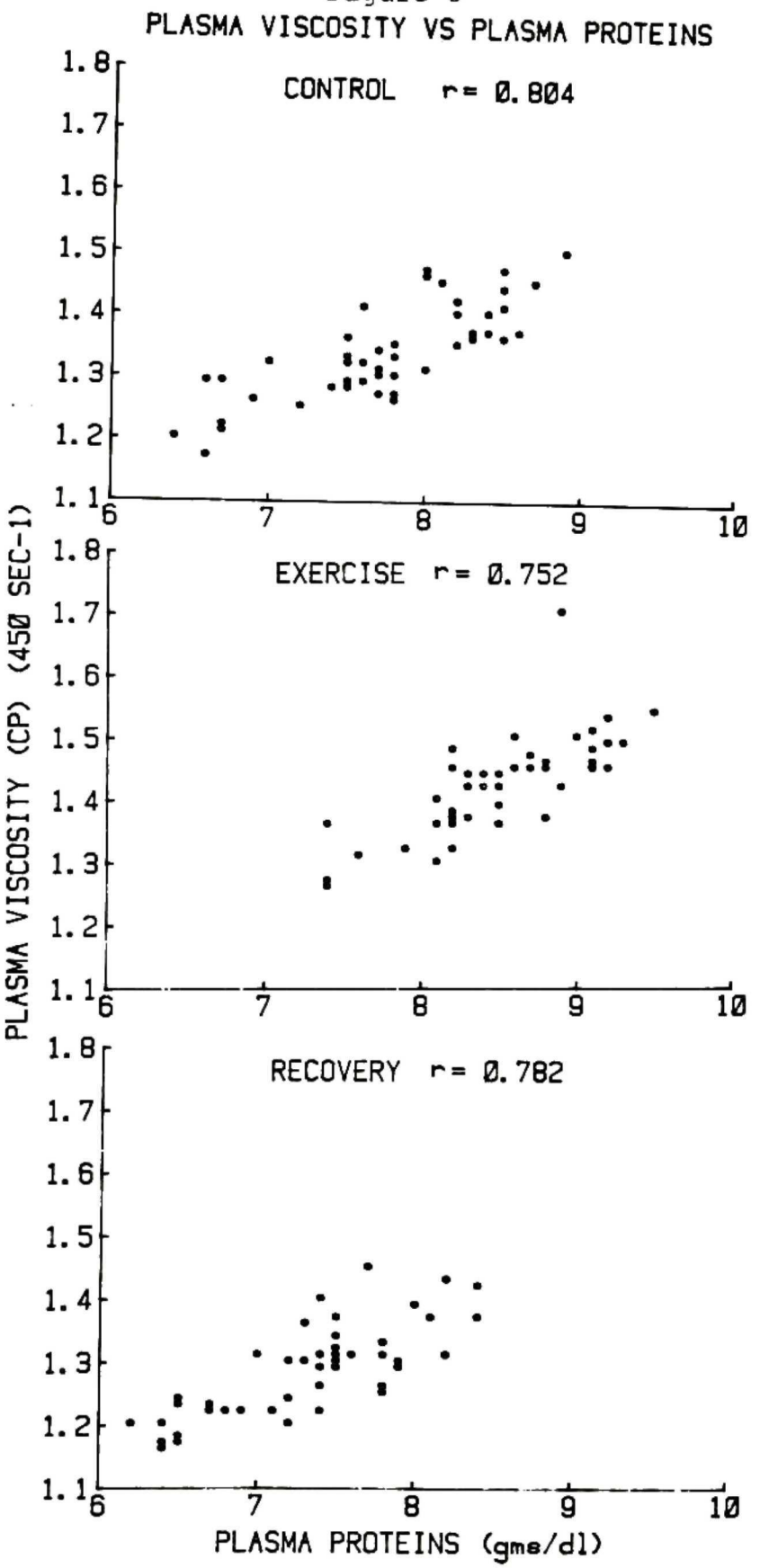

PLASMA VISCOSITY VS PLASMA PROTEINS
CONTROL r= 0.804
EXERCISE r= 0.752
RECOVERY r= 0.782
PLASMA VISCOSITY (CP) (450 SEC-1)
PLASMA PROTEINS (gms/dl)
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
6
7
8
9
10

Figure 9. Plasma Viscosity vs Fibrinogen Concentration. This scatter plot demonstrates a moderate correlation between plasma viscosity and fibrinogen concentration at control (r=.576), exercise (r=0.553) and recovery (r=0.526) samples for the 47 women in the study group. All correlations were significant at the $p < 0.01$ level.

Figure 9

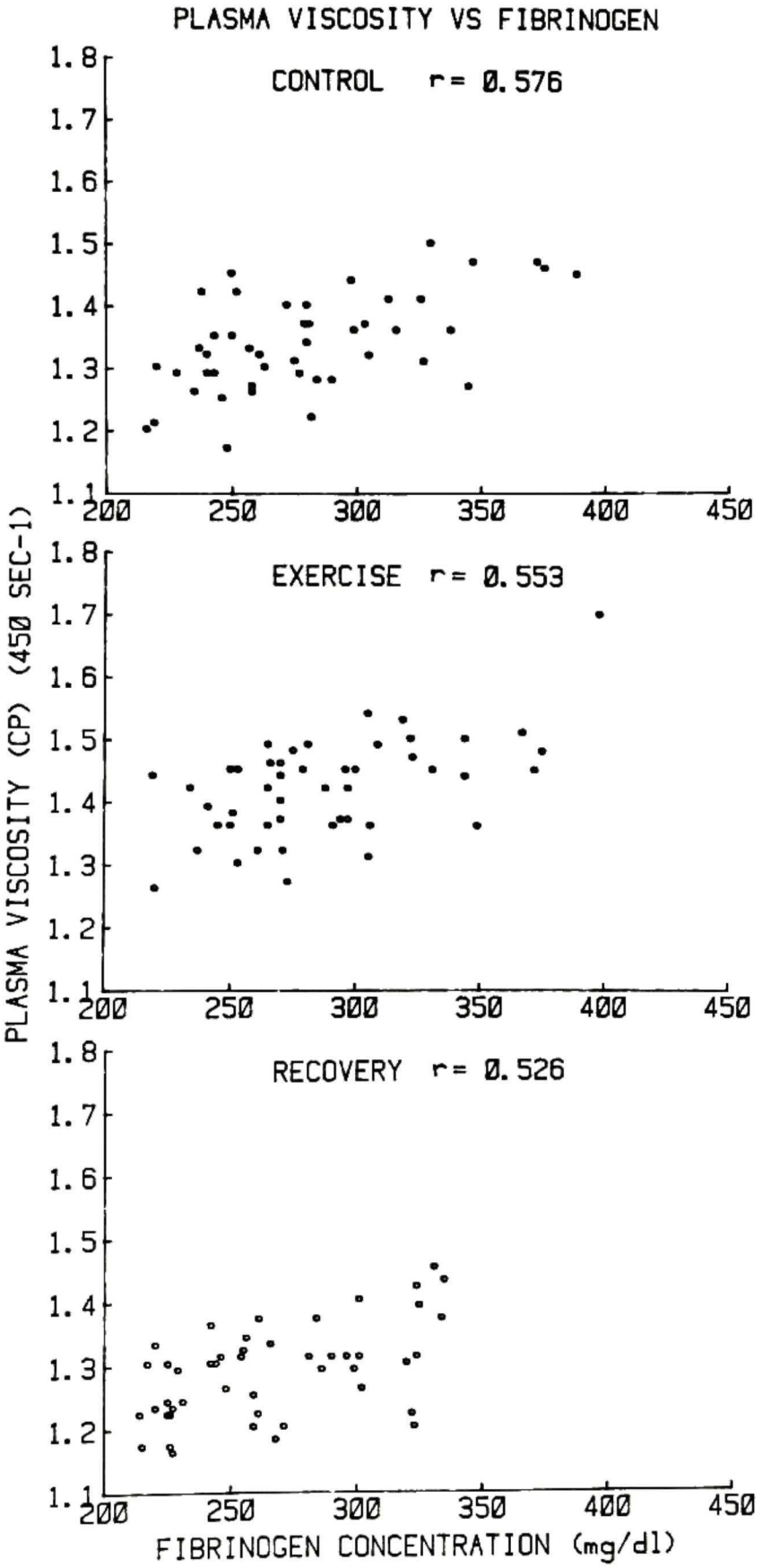

PLASMA VISCOSITY VS FIBRINOGEN
CONTROL r= 0.576
EXERCISE r= 0.553
RECOVERY r= 0.526
PLASMA VISCOSITY (CP) (450 SEC-1)
FIBRINOGEN CONCENTRATION (mg/dl)
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
200
250
300
350
400
450

Figure 10

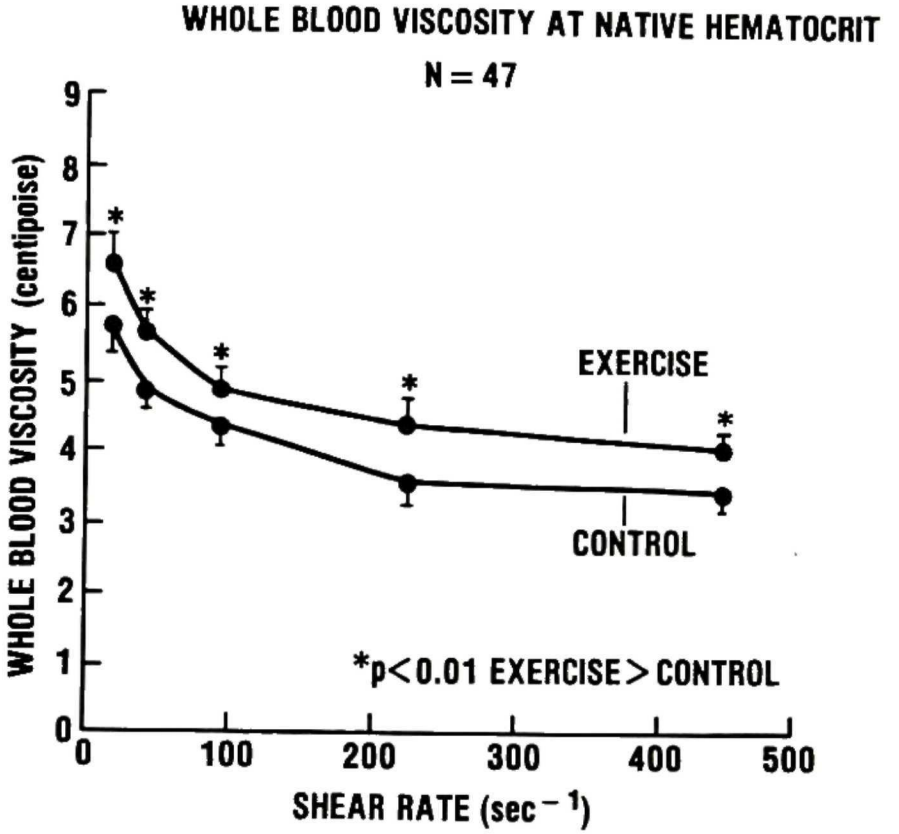


Figure 10. Whole Blood Viscosity at Native Hematocrit Control and Exercise. This graph demonstrates a decrease in whole blood viscosity with increasing shear rate. Whole blood viscosity was significantly greater $p<0.01$ after exercise in the 47 women at all shear rates. The brackets are $\pm$ S.E.M.

Figure 11

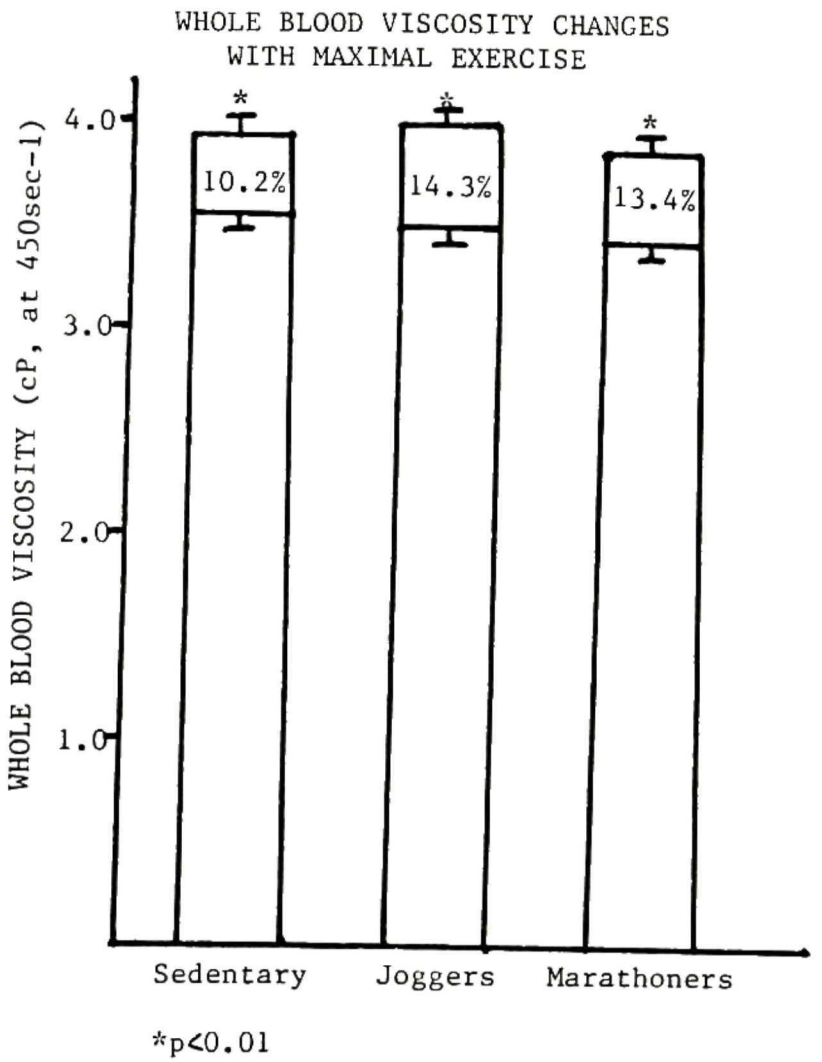


Figure 11. Whole Blood Viscosity (WBV) Change with Maximal Exercise. A significant increase in whole blood viscosity was observed in the (15) sedentary subjects, (14) joggers, and (18) marathoners. The lower bar represents the control value, the upper bar the exercise value. The brackets are $\pm$ S.E.M. The asterisks denote the significance of the difference between control and exercise values.

Figure 12

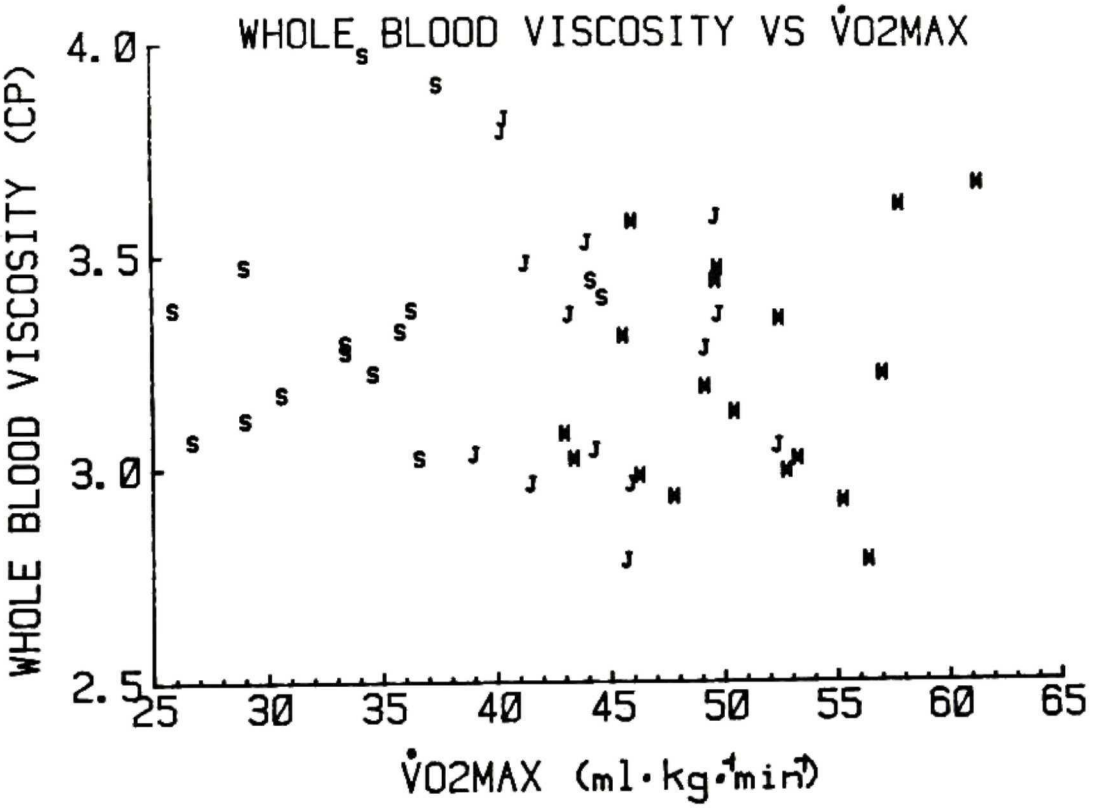


Figure 12. Whole Blood Viscosity at Native Hematocrit vs $\dot{V}O_2$ Max. There was no correlation between whole blood viscosity (cP, at 450 sec^{-1}) and aerobic capacities ($ml \cdot kg^{-1} \cdot min^{-1}$) for the 15 sedentary subjects (S), 14 joggers (J), or 18 marathoners (M).

Figure 13. Whole Blood Viscosity vs Hematocrit. This scatter plot demonstrates a positive correlation between whole blood viscosity and hematocrit of (r=0.835) control, (r=0.828) exercise, and (r=0.814) for recovery samples for the 47 women in the study group. All correlations were significant at the $p < 0.01$ level.

Figure 13

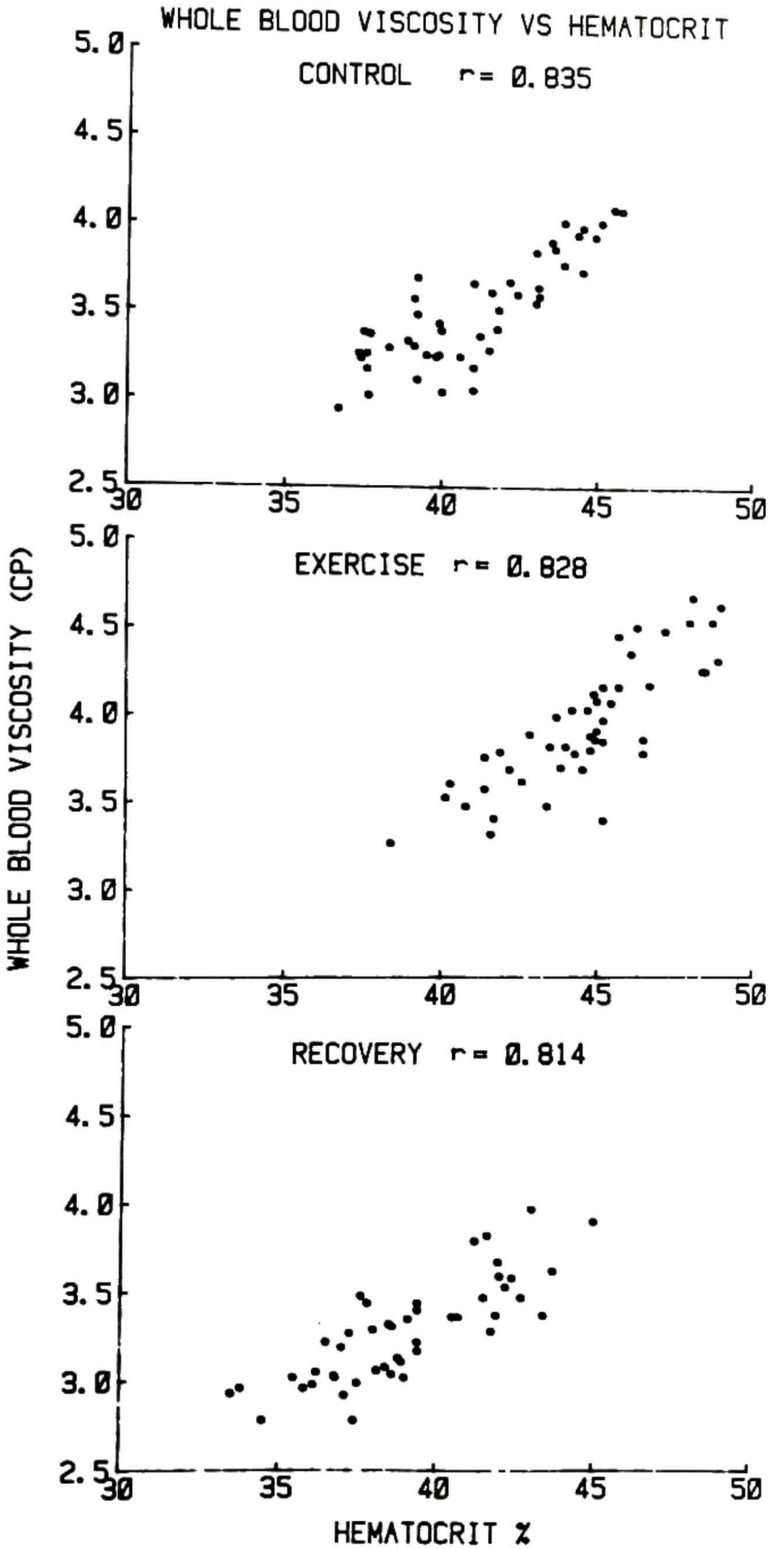

WHOLE BLOOD VISCOSITY VS HEMATOCRIT
CONTROL r= 0.835
EXERCISE r= 0.828
RECOVERY r= 0.814
WHOLE BLOOD VISCOSITY (CP)
HEMATOCRIT %
5.0
4.5
4.0
3.5
3.0
2.5
30
35
40
45
50

Figure 14

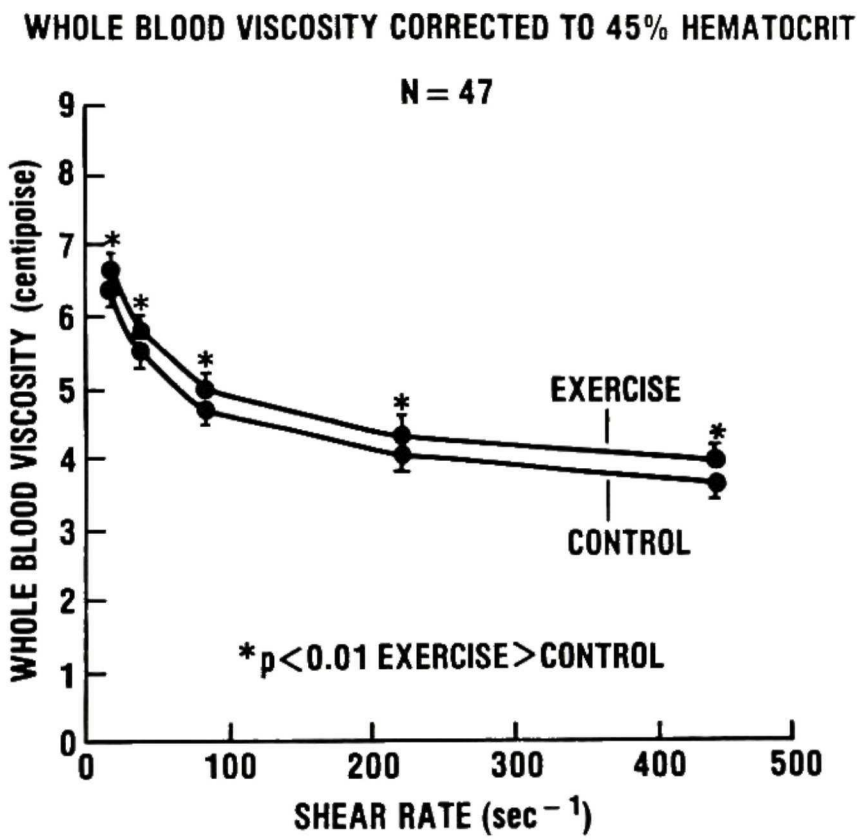


Figure 14. Whole Blood Viscosity Corrected to 45% Hematocrit (WBV45) Exercise and Control. For all individual samples the hematocrit was corrected to 45% (± 0.2%) with autologous plasma (WBV45) for control and exercise samples and measured in cP at 450 sec^{-1}. Values plotted are means ± S.E.M. WBV45 was significantly greater after exercise in the 47 women at all shear rates.

Figure 15

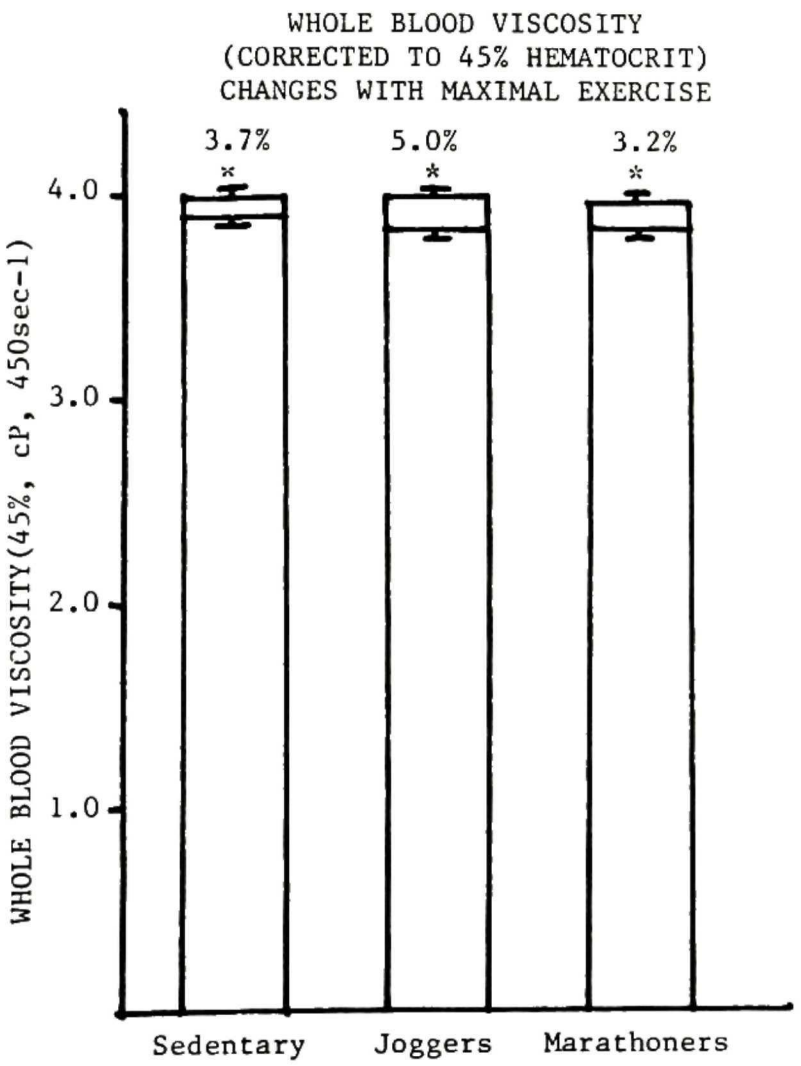


Figure 15. Whole Blood Viscosity Corrected to 45% Hematocrit (WBV45) Changes with Maximal Exercise. A significant increase in WBVc was observed in the 15 sedentary subjects, 14 joggers, and 18 marathoners. The lower bar represents the control value and the upper bar represents the exercise value. The brackets are ± S.E.M. The asterisks denote the significance of the difference between control and exercise values.

Figure 16. ESRc vs ZSR. This scatter plot demonstrates strong positive correlations between these two methods of determining red cell aggregability. The correlations between ESRc and ZSR were ($r=0.859$) for control, ($r=0.729$) for exercise and ($r=0.747$) for recovery samples for the 47 women in the study group. The correlations were significant at the $p < 0.01$ level.

Figure 16

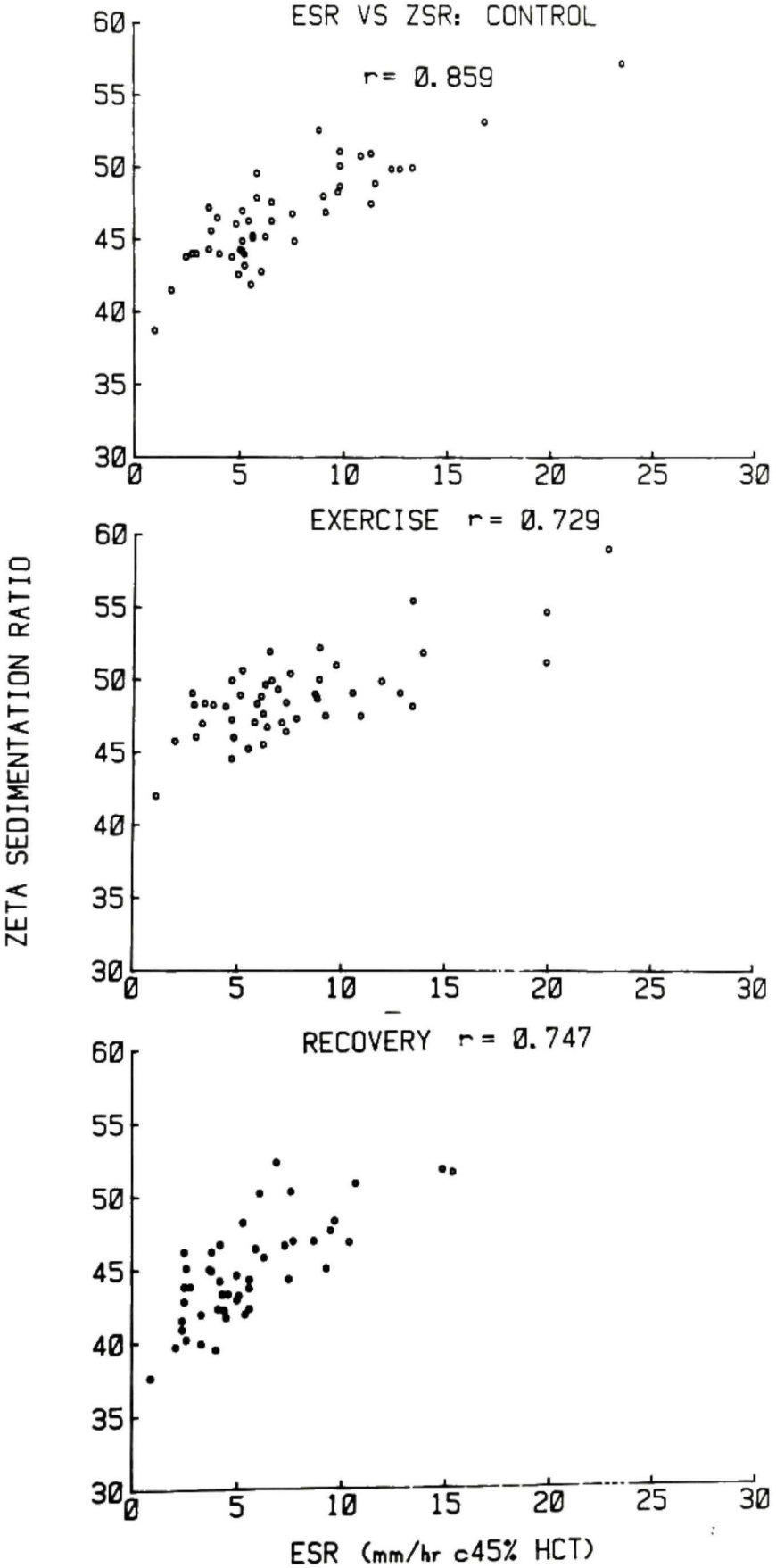

ESR VS ZSR: CONTROL
r= 0.859
EXERCISE r= 0.729
RECOVERY r= 0.747
ZETA SEDIMENTATION RATIO
ESR (mm/hr c45% HCT)
60
55
50
45
40
35
30
0
5
10
15
20
25
30

Figure 17. Fibrinogen Concentration vs Erythrocyte Sedimentation Rate (corected to 45% and 1.3 cP). This scatter plot demonstrates positive correlations between fibrinogen concentration (mg/dl) and ESRc for control (r=0.787), exercise (r=0.601), and recovery (r=0.579) samples for the 47 women in the study group. All correlations were significant at the $p < 0.01$ level.

Figure 17

FIBRINOGEN VS ESR:

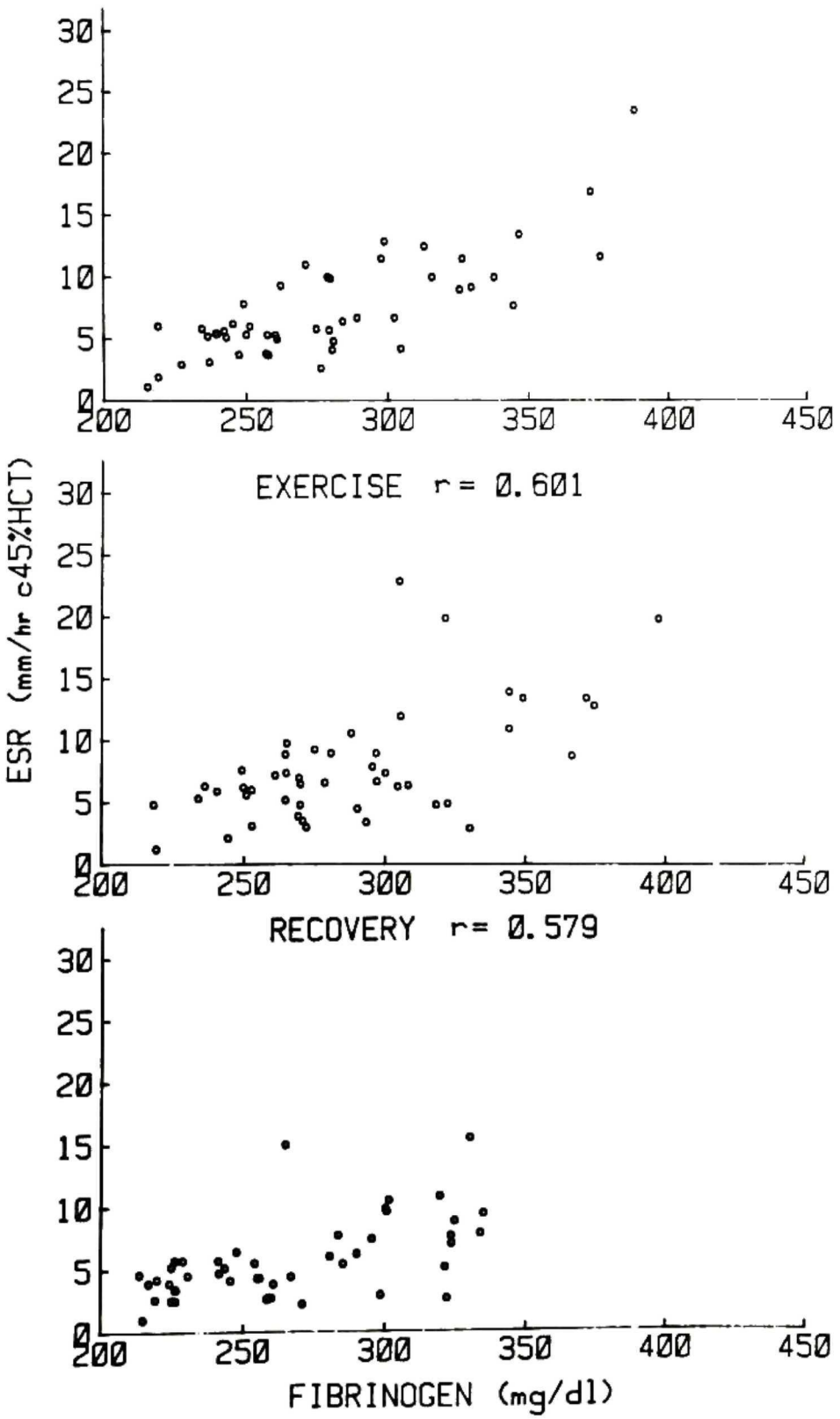


Figure 18. Fibrinogen Concentration vs Zeta Sedimentation Ratio (ZSR). This scatter plot demonsrates positive correlations between fibrinogen concentration (mg/dl) and ZSR of (r=0.697) for control, (r=0.456) for exercise and (r=0.609) for recovery samples for the 47 women in the study group. All correlations were significant at teh $p < 0.01$ level.

Figure 18

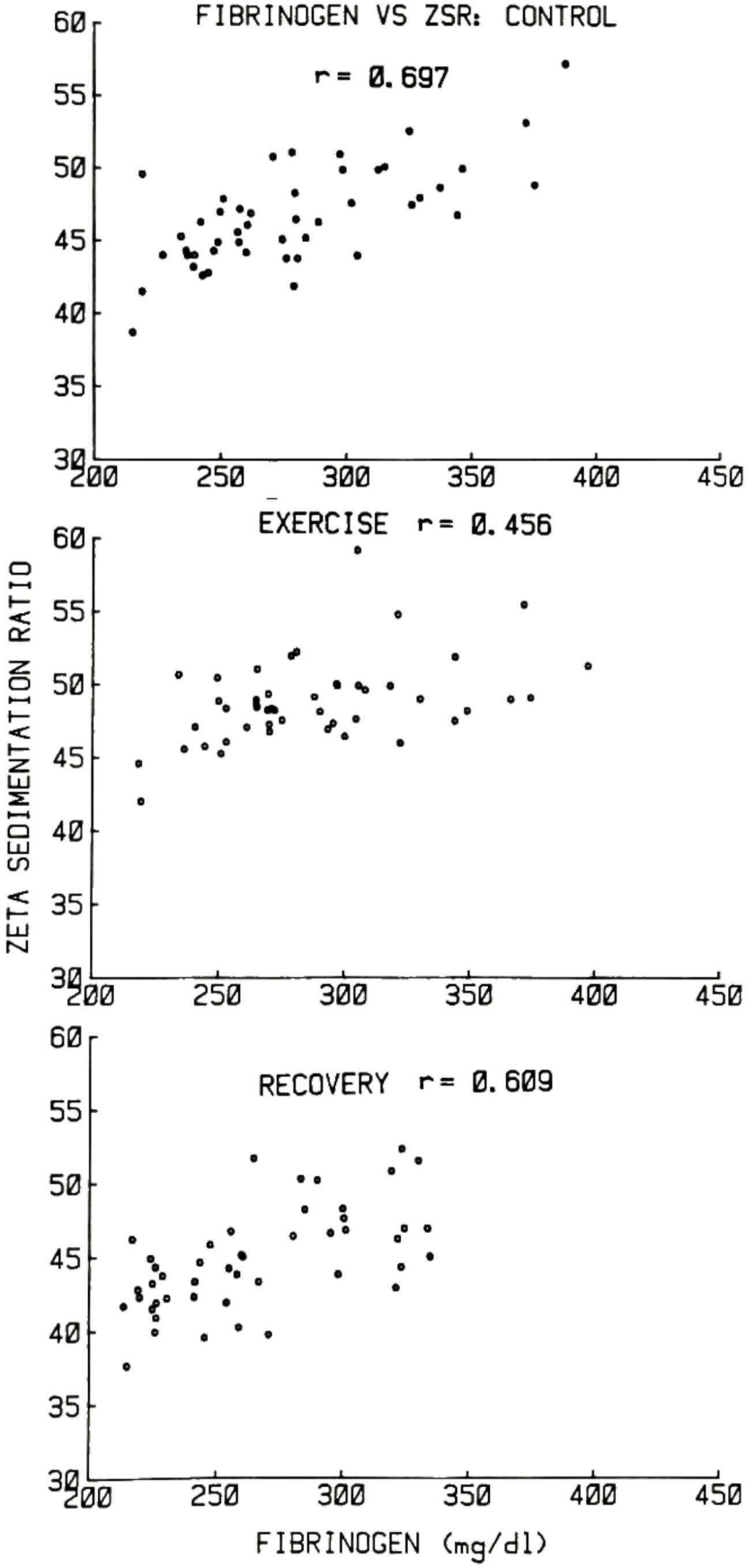

FIBRINOGEN VS ZSR: CONTROL
r = 0.697
EXERCISE r = 0.456
RECOVERY r = 0.609
ZETA SEDIMENTATION RATIO
FIBRINOGEN (mg/dl)
60
55
50
45
40
35
30
200
250
300
350
400
450

Figure 19

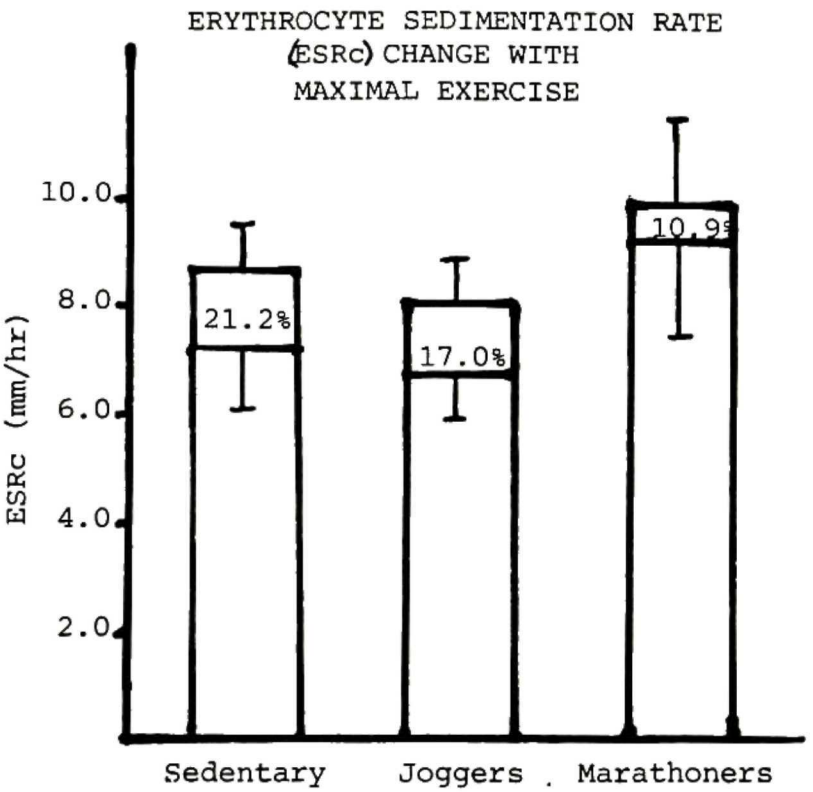


Figure 19. Erythrocyte Sedimentation Rate Corrected to 45% Hematocrit and 1.3 cP (ESRc) Change with Maximal Exercise. Increases in ESRc with exercise were not significant for (15) sedentary subjects, (14) joggers or (18) marathoners. The lower bar represents the control values, the upper bar the exercise value. The brackets represent $\pm$ S.E.M. There were no differences in control ESRc or percentage increase in ESRc with exercise among groups.

Figure 20

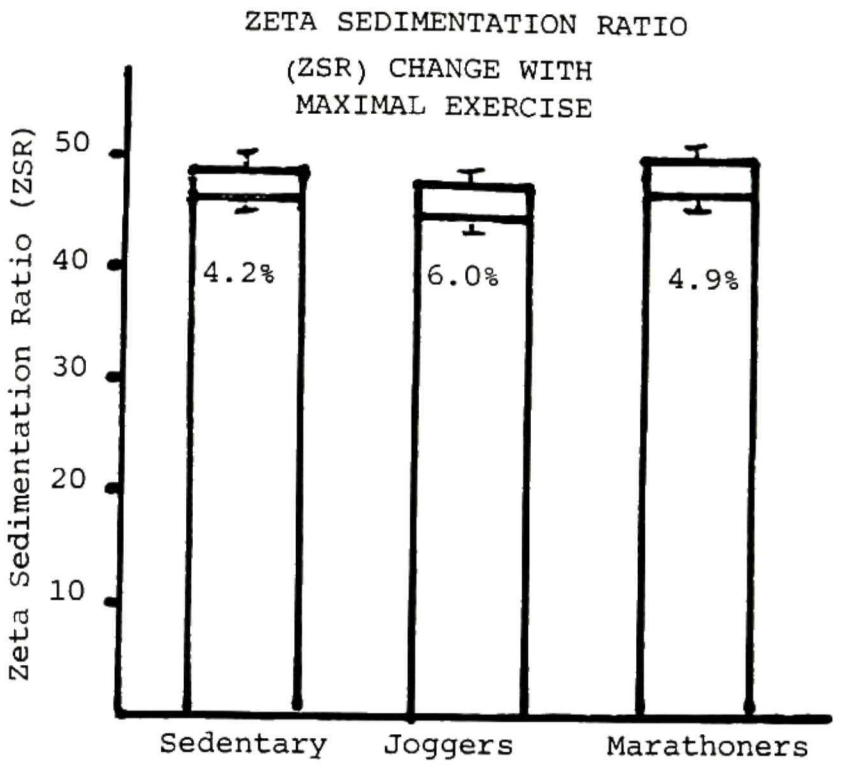


Figure 20. Zeta Sedimentation Raio (ZSR) Change with Maximal Exercise. Increases in ZSR with exercise were not signifiant for (15) sedentary subjects, (14) joggers, or (18) marathoners. The lower bar represents the control values, the upper bar the exercise value. The brackets represent $\pm$ S.E.M. There were no differences in control ZSR or percentage increase in ZSR with exercise among the groups.

Discussion

The Control of Key Variables in the Study Population

A common failing of the few previous studies involving blood viscosity changes with fitness level is the poor documentation and classification of the study population. In this study much effort was taken to obtain a very well matched subject pool, the members of which differed only in conditioning level.

As will be discussed in greater detail below, factors felt to be critical for the measurement of both conditioning and blod viscosity ($\dot{V}O_2$ max, body habitus, timing of sampling, age) were all carefully controlled in this study. In previous studies, fitness level was either not reported, arbitrarily or reported only indirect measurements were made.[16,28,54,55,71,75,95,116] This study evaluated women in three distinct conditioning groups and directly measured their maximal aerobic capacities. Direct aerobic capacity measurement is the single most reliable method for predicting maximal aerobic endurance performance.[7,29,138]

Since $\dot{V}O_2$ max is directly related to frequency, intensity and duration of training it is expected that the marathoners would have the highest $\dot{V}O_2$ max followed by the joggers.[4] The $\dot{V}O_2$ max was 33% greater in our marathoners than in our sedentary subjects. Increases in $\dot{V}O_2$ max of greater than 25% have been recorded in training programs.[4] These increases are often, in part, a result of a net loss of

body fat and an increase in lean body mass, and are not just due to circulatory changes that occur with conditioning.[4]

Attempts were made to closely match subjects for body habitus. It was especially difficult to find sedentary subjects as lean as the conditioned athletes. However, the three groups were similar in height, weight, and lean body mass. It should be noted that all groups were well below reported averages for body fat in American women with ages similar to the study group.[31,166] For this reason, even our sedentary group had a mean VO_2 max that placed them in a fairly good fitness category.

Since many circadian, seasonal and other temporal changes may affect whole blood viscosity it was necessary to control for these also. The time of day at which the samples were taken was not always mentioned in previous studies.[75] Since plasma volume, the concentrations of various plasma proteins, and hematocrit show a diurnal variation it is important to sample all subjects at the same time of the day.[136] In this study all blood samples were obtained between 7:45 A.M. and 11:45 A.M. to minimize possible variation due to circadian rhythms.

Seasonal variations have been reported in blood viscosity.[12,119] Because plasma volume expansion and decreased hematocrits may occur in summer, beginning a conditioning study in late spring may bias the outcome of the study. In this study all samples were obtained from late fall to early spring and participants among the three

conditioning groups were randomly accepted during the study.

Cyclic variations in blood viscosity during the menstrual cycle have been reported.[12] At low shear rates marked differences were apparent. However, at the shear rates that were measured in the present study very little variation occurs in blood viscosity during the menstrual cycle. To eliminate the possible effect of these cyclic variations, all subjects were tested 5-10 days after the onset of menses (early follicular phase).

Age is not thought to markedly affect any of the key factors affecting whole blood viscosity. However, one report suggests higher fibrinogen concentrations with advanced age.[58] It is also well known that age significantly affects aerobic capacities, with aerobic capacity decreasing with age.[86] Previous studies have had wide variations in the ages of the subjects. This study group had a very narrow age range and the mean ages for the three conditioning groups were comparable.

In summary, the subject population was carefully chosen and well-characterized by fitness level and aerobic capacity. No other study evaluating blood viscosity alterations with exercise have employed such a tightly controlled, selected population. In addition, subjects were sampled under strictly controlled conditions to limit other temporal (diurnal, menstrual, seasonal) variations in blood viscosity which may occur.

The Impact of Sampling Procedures on the Experimental Outcome

Many of the observations made during the course of a treadmill run were altered by the sampling of blood. Removal of 45-50 cc of blood for control and exercise samples affected measurements of WBV in exercise and recovery samples, respectively. In the average 55 kilogram subject with a blood volume of four liters this represented a two percent loss of red cells. If the entire loss of red cells and plasma was replaced by interstitial water the recovery sample would show a four percent decrease in hematocrit, as well as a six percent decrease in plasma protein concentration. Our recovery sample data agreed closely with these calculations. An overall 4.6% decrease in hematocrit coupled with a 5.2% loss in total plasma proteins was observed. The native hematocrit WBV decreased almost 6.0% while WBV45 was down 2.1%.

These changes suggest a rapid redistribution of plasma volume, within an hour of exercise replacing the intravascular losses which maximal exercise induces. These data are consistent with previous work which demonstrated a rapid return of plasma water to the vascular spaces. A return of hematocrit and plasma volume to control values therefore occurs rapidly after completion of exercise.[101]

Hemoconcentration With Exercise

A marked hemoconcentration (8.9% increase in hematocrit) was observed with maximal exercise for the entire group. This degree of hemoconcentration is consistent with several previous studies in men in which the hematocrit increased

from 4% to 10% with maximal exercise.[48,95,114,156]

In man, red cell mass does not increase or decrease with exercise. Therefore, any increase in the hematocrit must be due to a loss of plasma volume.[89,115] Decreases in plasma volume can be calculated from changes in hematocrit using equations derived by Van Beaumont.[155] Van Beaumont has reported these calculations to be accurate to within 3% of measured plasma volumes.[155] Using these equations we found a 12.7% decrease in plasma volume for the study group.

Van Beaumont has previously reported a 9.7% increase in hematocrit with exercise paralleled by a 9.6% change in hemoglobin concentration and a 9.2% change in red blood cell count. He concluded that with maximal exercise the percent change in plasma volume could be calculated using either of these variables. These calculations are accurate if the red cells remain the same size after exercise.[48,156,157,158,159] Later studies have pointed out, however, that red cells can shrink, remain stable or swell depending upon the osmolality and pH changes at maximal exercise.[160] Red cell volume changes with exercise would affect hematocrit determinations and, therefore, plasma volume calculations based upon hematocrit. In this study the MCV was significantly higher after exercise. As a result the increases in hemoglobin concentration (6.8%) and in red cell count (6.1%) (which were based on hemoconcentration and not influenced by MCV), were less than the increase in hematocrit (8.9%). The equation by Dill which takes into account changes in hemoglobin concentration,

as well as hematocrit, seems to be more appropriate in evaluating plasma volume loss with exercise.[52] Using these calculations we observed an 11.0% loss in plasma volume. By either Dill's or Van Beaumont's method the degree of plasma volume loss was comparable among the groups (Table 4). Thus hemoconcentration appears to be a function of the relative intensity of the work (maximum work) rather than the absolute work performed and does not seem to be influenced by the degree of aerobic conditioning.

Hemoconcentration with exercise elevates the plasma protein concentrations, as well as hematocrit. The 10.2% increase in plasma protein concentration observed for the entire study group was consistent with previous studies.[114,160] In earlier studies it was assumed that the plasma proteins remained in the vasculature with exercise. However, later studies have reported plasma protein loss from the vasculature.[51,157] The amount of protein lost appears to be a function of the intensity, duration, and method of exercise.[48,137,157] The loss of plasma proteins from the vasculature is still minor when compared with the marked increase in plasma protein concentration that is due to the acute loss of plasma water with exercise.

Fluid shifts with exercise are due to the transcapillary movement of plasma water into exercising muscles. This is a result of hyperosmolarity of the tissues and increased capillary hydrostatic pressures.[101] It has been shown that most of the plasma water shift occurs within the first six

minutes of exercise and the degree of fluid shift is a function of the relative intensity rather than the duration of exercise.[111]

As stated above plasma volume loss was 11.0 to 12.7%. However, protein concentrations increased only 10.2%. This suggests a small net loss of plasma proteins from the vasculature with maximal exercise. The concentration of plasma solute is related to the change in plasma volume. As discussed earlier the plasma volume was estimated by two equations. Therefore, two equations were also used to calculate the loss in plasma protein content.[79,157] The calculated losses of 1.9-3.7% in total plasma proteins with maximal exercise are in close agreement with previous findings.[48,137,157] This protein loss was similar among the groups and was a function of the relative intensity of exercise and not the duration.

Of particular interest was the relatively small increase in fibrinogen concentration (3.7%) and the disproportionately large loss of fibrinogen content (7-9%) with maximal exercise. This has several important implications for changes in blood viscosity with exercise.[40,154]

In discussing whole blood viscosity changes with exercise it is necessary to separate the various components of blood viscosity and evaluate each in detail. Therefore, the contribution and effects of hematocrit, plasma viscosity, aggregability and red cell deformability will be approached separately before whole blood viscosity will be addressed.

Hemoconcentration produced by exercise increases hematocrit and plasma protein concentrations, causing important rheologic perturbations which will now be examined.

Blood Viscosity Response to Exercise:

Hematocrit

Changes in hematocrit were strongly correlated with changes in whole blood viscosity, in control, exercise and recovery samples (Figure 10). In addition, the relative contribution of hematocrit to total whole blood viscosity was the same at rest, after exercise and after recovery.

It is a well-established observation that the hematocrit in most species remains very close to that defined as optimal for *in vitro* estimates of maximal hemoglobin transport.[50,146] As hematocrit increases so does viscosity. A certain end-point is reached for hematocrit at which the amount of oxygen and hemoglobin delivered per unit of time will no longer increase because of increased viscous resistance and reduced flow.[146] Decreases in flow thus offset increases in oxygen carrying capacity. The normal hemoglobin concentration in women is less than that in men. The optimal hematocrit for maximal hemoglobin delivery is near the resting hematocrit.[145] However, as shear stresses increase with exercise, because of the tremendous increase in cardiac output, the optimal hematocrit for oxygen transport also increases.[154] The modest 6-9% increase in hematocrit and hemoglobin concentration we observed may be an adjustment towards the optimum for maximal oxygen delivery during exercise.

Adams found that total body hemoglobin was the blood variable which most strongly correlated with VO_2 max ($r=0.85$).[1] He suggested that the lower VO_2 max in highly conditioned women compared to highly conditioned men was primarily due to the lower total body hemoglobin in women rather than a lower cardiac output or oxygen extraction at the tissue level. These data suggest that women have a lower than optimal hematocrit for maximal efficiency of oxygen delivery.

In the present study, the hematocrit and hemoglobin concentrations at rest were similar in the three fitness categories. In a previous study in this laboratory similar hematocrits were also recorded in 60 men in three distinct conditoning groups.[9] However, other workers have reported a decreased hematocrit with conditioning which is probably the result of a greater increase in plasma volume relative to red cell content.[17,27]

Plasma Viscosity Changes with Exercise

This study showed that the increase in plasma viscosity was much less than would be expected from the degree of hemoconcentration if only plasma water were lost to interstitial spaces. With maximal exercise the increase in plasma viscosity was similar among the groups and averaged only 6.3%. Total plasma proteins increased more than 10%. Most of the increase was in the albumin and globulin fractions, while the rise in fibrinogen concentration was relatively slight. This 3.7% increase in fibrinogen concen-

tration was considerably less than would be expected from the degree of hemoconcentration. As will be discussed, this change in fibrinogen concentration may aid in the attainment of maximal oxygen transport during vigorous exercise.

This study demonstrated that the disproportinately small rise in fibrinogen concentration was largely responsible for the blunted increase in plasma viscosity. This smaller than expected rise in fibrinogen concentration has several rheological consequences which are advantageous in the exercising subject. If the fibrinogen concentration had increased as much as hematocrit and hemoglobin, even more marked increases in plasma viscosity would have occurred. As hematocrit increases, oxygen transport is augmented. However, increases in plasma viscosity increase whole blood viscosity and decrease flow, thus decreasing oxygen transport.[32,135]

It is physiologically advantageous and more efficient for oxygen delivery to only increase plasma viscosity by only 6.3% during maximal exercise while incurring an 11.0% loss in plasma volume. This blunted increase in plasma viscosity with exercise was most likely due to a relatively large loss of fibrinogen from the vasculature, since the loss of albumin and globulin was relatively small.

Previous investigators have suggested that the mechanism for maintaining the fibrinogen concentration at near pre-exercise levels during exercise induced hemoconcentration is increased fibrinolytic activity.[95] It is well-documented that fibrinolytic activity is markedly accelerated with

exercise.[44,45,72,73,80] However, whether or not accelerated fibrinogenolysis occurs with exercise is controversial. Collen et al. have reported increases in the degradation of fibrinogen with exercise, but Ferguson et al. and Gurewich et al. have been unable to document any increased fibrinogen catabolism with exercise.[45,73,80] The fibrinogen chain most susceptible to degradation (A-alpha chain) showed no increased degradation after exercise and the ratio of total alpha-chain to beta and gamma chains after exercise was unaltered.[73] If fibrinogenolysis does not occur fibrinogen must be lost by another mechanism. Two hypotheses which may explain this include removal of fibrinogen from the plasma by transudation into the interstitial spaces and increased fibrin clot formation with exercise. Of the two, an increased deposition of fibrin clots during exercise is the most likely explanation for the observed changes in fibrinogen concentration.[72]

Regardless of the mechanism for attenuation of the increase in fibrinogen and total plasma protein concentrations during hemoconcentration, definite rheological advantages are apparent. In the microvasculature, because of central migration of red blood cells, relatively large plasma cuff, and hematocrits of 8-20%, cellular components make a relatively minor contribution to whole blood viscosity when compared to plasma. Therefore, plasma viscosity is the major determinant of blood viscosity in the microvasculature.[81] With exercise an increase in hematocrit and hemoglobin con-

centration should occur in the microvasculature while a slight increase in plasma viscosity would also be expected.

Plasma Viscosity Changes with Conditioning

With endurance training multiple alterations occur which increase oxygen delivery and utilization.[7.131] Little is known about possible effects of conditioning on plasma viscosity. However, a decrease in plasma viscosity in endurance trained individuals at rest and exercise would certainly increase oxygen delivery. Letcher found significantly lower plasma viscosities in subjects (12 males, 1 female) who ran 20-70 miles per week compared to plasma viscosities of sedentary subjects (11 male, 1 female). The difference was primarily due to a lower fibrinogen concentration in the runners.[95] However, in the present study involving 47 women, there were no significant differences in plasma viscosity among the three conditioning groups. Marathoners had a higher fibrinogen concentration than the other groups. Even though the women running higher mileages had increased fibrinogen concentrations, their plasma viscosities were no different than those of the other groups. Fibrinogen concentration has the most influence of any single protein fraction on plasma viscosity. However, total plasma protein correlated more closely with plasma viscosity ($r=0.804$). The lack of a rise in plasma viscosity is therefore not surprising since the marathoners total plasma protein concentrations were similar to the other groups. If a single variable model is adopted to predict plasma viscosity from plasma protein

concentrations then $r^2 = 0.64$. This means that 36% of the total variability in plasma viscosity is still unexplained. The total protein concentrations were not significantly different in the marathoners and sedentary subjects. In this cross-sectional study of women, aerobic conditioning was not associated with differences in plasma viscosity and long-distance training did not have an effect on fibrinogen concentration.

Red Cell Aggregability with Exercise and Conditioning

As stated earlier, aggregability of red cells is influenced by hematocrit, plasma protein concentrations (especially fibrinogen) and shear stresses at the cell surface.[154] In this study, marked increases in hematocrit and plasma proteins with exercise resulted in significantly elevated ESRc and ZSR (Table 12). For the total group, ZSR increased 5.0% and ESRc 16.6% (Table 7).

The increase in hematocrit with exercise increases crowding of individual cells and increases cell to cell interaction. Though not directly measured, presumably macromolecular bridging increases and aggregates form more readily.

Fibrinogen has the most influence on aggregability. The results of this study are consistent with previous work showing a strong correlation of ESRc and ZSR with fibrinogen concentration ($r=0.790$ and $r=0.697$, respectively, $P < 0.01$). Because of the strong positive correlation of fibrinogen concentration with sedimentation rates, the modest increase in

fibrinogen (3.7% in total group) after exercise still contributed to the increased aggregability. The effects of increased hematocrit and increased fibrinogen concentration on red cell aggregability are additive.

Prior studies on physical conditioning and red cell aggregability are quite limited. Dintenfass reported normal values for an aggregability index based upon sedimentation methods as 109.8 ± 73.6; a mean value of 40.9 ± 34.0 was found for nine athletes.[53] Letcher found a lower fibrinogen concentration in male athletes versus sedentary subjects which could be associated with decreased aggregability.[95] Other studies suggest that the erythropoetic system is more active in men who train heavily and have increased red blood cell destruction and more rapid erythrocyte turnover rates. This would result in a younger red blood cell population.[126,129] However, these training regimens were severe and proper studies have not been done to determine if athletes indeed have a younger red cell population. Younger cells contain a greater number of sialic acid residues and possess a greater zeta potential which acts to repel other red cells.[102] The zeta potential decreases with aging of cells resulting in an increase in macromolecular bridging.[154]

The trends of the magnitude and direction of the changes in the ESRc and ZSR were those expected among the conditioning groups, given the higher fibrinogen concentrations in the marathoner group. However, the variations in ESRc and ZSR were too great to allow statistical significance. In this

study the fibrinogen concentration in marathoners was greater than in joggers or sedentary subjects. Since fibrinogen concentration correlated strongly with ESRc and ZSR, a higher sedimentation rate would be expected in the marathoners. However, the apparently higher ESRc of 9.3 ± 6.5 mm/hr in marathoners versus 7.0 ± 2.8 mm/hr in sedentary and 6.5 ± 3.2 mm/hr in joggers was not statistically significant. Likewise the ZSRs were not statistically different among the three groups (47.5 ± 4.0 in the marathoners; 45.6 ± 3.4 in the joggers; and 46.7 ± 2.7 in the sedentary).

In summary, with exercise, in vitro methods reflect significant increases in aggregability which correlate with fibrinogen concentration and increased hematocrit. However, in this cross-sectional study in women, conditioning did not appear to play a significant role in the aggregability of red cells.

Red Cell Deformability and Exercise

Another major determinant of whole blood viscosity is the flexibility or deformability of the red cells. The fluid droplet-like behavior of cells in suspension is responsible for a decrease in whole blood viscosity with increasing shear rates, and also allows the cells to pass through passageways smaller than their diameter.[33,132]

Exercise is thought to decrease deformability of red cells by decreasing pH and PO_2, and increasing the osmolality of the intravascular spaces.[101] In normal individuals the degree of red cell stiffening which occurs in the micro-

vasculature with exercise may be difficult to quantify. In certain pathological conditions such as the sickling diseases, exercise may actually result in a decreased flow to an exercising leg as a result of markedly decreased deformability of the cell with decreasing oxygen content and lower pH.[37] As stated earlier, the degree of pH reduction and increase in osmolality seems to be a function of the relative intensity of the exercise and the resultant build up of metabolites, rather than the absolute work load.[76,157]

In previous studies osmolality and pH correlate strongly with lactate concentrations.[48,157] Immediately after exercise lactate concentrations were more than eight times the control levels. Such changes in pH and osmolality may have significant effects on cell size.[48,157] With maximal exercise an increase in the mean corpuscular volume of red cells was recorded in the present study. Mean corpuscular hemoglobin concentration decreased and plasma hemoglobin concentration increased less than the hematocrit. This swelling of red cells causes a reduction in the surface area to volume ratio. Previous studies have reported decreased filterability and deformability of cells with decreased surface area to volume ratios.[106] In the present study the relative change in deformability of the cells before and after exercise could not be measured directly. However, the effect of aerobic conditioning on the flexibility of the red cell population was evaluated indirectly.

Red Cell Deformability with Conditioning

During strenuous conditioning increased red blood cell turnover (both increased destruction and increased production of erythrocytes) is thought to occur.[129] Higher reticulocyte counts in athletes are not unusual. The younger red blood cells possess a larger surface area to volume ratio, as well as lower calcium and higher ATP levels.[150] These factors all increase flexibility of the cell.

Several studies involving cardiovascular diseases or "less fit" individuals with angina, myocardial infarction, intermittent claudication and sickle cell disease have demonstrated a decreased deformability or filterability of red blood cells.[38,59,62,67,127] When red cells are suspended at a standard cell concentration (45% HCT) in a medium of standard viscosity, the WBV at high shear rates (where total dispersion of the cells exists) is a good measure of the deformability of red cells. Differences in deformability of red cell populations in normal versus sick patients are easily measured.[135] However, in a population of normal subjects differences in deformability of red cells may be too subtle to detect by this method.

In the present study, to evaluate the differences in deformability among the conditioning groups, hematocrits were standardized to 45% with autologous plasma and WBC45 was measured at high shear rates (450 sec^{-1}). The plasma viscosities (suspending media) were similar in the three groups. In addition the shear rate was well above the 50 sec^{-1} required for total dispersion of aggregates.[93] There-

fore, any major differences in blood viscosity would be due to the deformability of the cells in suspension. However, the WBV45 was similar in samples at rest for all three groups. Therefore, if any differences did exist they were too small to detect by this indirect method for the determination of red cell deformability.

Whole Blood Viscosity

Red cells suspended in plasma exhibit non-Newtonian characteristics with very high blood viscosities at lower shear rates (Figure 2). The lowest shear rates measured (11.25, 22.0, and 45 sec^{-1}) were low enough for aggregability of the cells to influence viscosity. However, at the three higher shear rates only the hematocrit, plasma viscosity and red cell deformability influenced viscosity. Multiple linear regression analyses with whole blood viscosity as the dependent variable, confirmed previous work showing that hematocrit exerts the major influence on whole blood viscosity with total plasma protein concentration also contributing significantly.[14] Hematocrit (packed cell volume) and total plasma proteins were responsible for most of the differences in whole blood viscosity when rest, exercise and recovery samples were compared.

Whole Blood Viscosity with Exercise

With exercise, hematocrit and plasma protein concentrations increased and whole blood viscosity markedly increased. With exercise hematocrit rose from 41.0 to 44.6 percent (8.9% increase from resting values), while whole blood viscosity

rose 12.6%. The greatest contributor to the elevated blood viscosity was the hematocrit. The increase in whole blood viscosity attributable to the increase in plasma viscosity was small, but significant. As a result, the increase in viscosity was more than would be expected from the increase in hematocrit alone. As discussed earlier the plasma viscosity did not increase as much as would be expected if only plasma water were lost because of a net loss of plasma proteins (especially fibrinogen). This was also true for whole blood viscosity.

In the few previous studies involving whole blood viscosity in a healthy population the results agree with those of the present study.[29,71,75] However, the elements of viscosity were not examined separately in these previous studies so comparisons cannot be made.

Whole Blood Viscosity with Conditioning

In this study aerobic conditioning did not affect whole blood viscosity. Whole blood viscosity did not differ significantly among the three groups nor did it correlate with aerobic capacity (Figure 21). Others have suggested an inverse correlation between fitness levels and blood viscosity.[29,54] However, the studies involving normal subjects were small, and poorly controlled. Multiple rheological abnormalities have been reported in patients with various cardiovascular diseases.[5,18] These include increased blood viscosity in hypertensive subjects due to increases in plasma viscosity, fibrinogen concentration and hematocrit.[62,94,113]

Patients recovering from myocardial infarction often have increases in hematocrit, plasma viscosity, fibrinogen concentration, and red cell aggregability, and decreases in red blood cell deformability.[36] Rheological measurements in the evaluation of patients have become a useful diagnostic indicator of impending circulatory problems and a prognostic tool.[36,53,160] Therefore, it is not surprising to see significant differences in blood viscosity factors in a group of "fit" subjects and a group of less fit subjects, when much of the latter group is comprised of subjects who are post-myocardial infarction patients, anginal patients or patients suffering from "low energy syndrome".[54,55]

Cardus and colleagues reported a decrease in blood viscosity after an eight week conditioning program in men. The decrease in blood viscosity was attributed primarily to a drop in hematocrit.[29] The major problems with Cardus' study was the failure to quantify aerobic capacity before or after the program. In addition, since hematocrit and blood viscosity may be lower in the summer months due to heat adaptation and plasma volume expansion, controls should have been included in this study to document that hematocrit changes were not due to seasonal variations.

Conclusion

In conclusion, multiple adaptations occur during aerobic conditioning to enhance oxygen delivery at rest and during exercise. However, in this cross-sectional study there appeared to be no adaptive adjustment in women to physical

conditioning that would augment oxygen delivery through a reduction in blood viscosity.

The results of this study do enhance our knowledge of blood viscosity changes with maximal exercise. With maximal exerise, increases in blood viscosity were observed which were greater than would be expected from the increase in hematocrit alone. However, the increase in blood viscosity was less than expected from the degree of hemoconcentration due to the loss of plasma proteins, especially fibrinogen from the vasculature with exercise.

VOLUNTEER AGREEMENT - Hematologic Alterations with Exercise in Women

This study is designed to assess blood clotting and other changes in the blood and blood elements with exercise and physical conditioning. These changes will be compared with changes in the cardiovascular (heart) and respiratory (breathing) systems and in the body's ability to handle heat stress with exercise and physical conditioning.

We will check blood samples before and after exercise. Not more than 50 ml (about 3 tablespoons) of blood will be drawn from a vein in your arm before and immediately after exercise. This may cause some discomfort or bruising of your arm. You will be exercised on a treadmill. The duration of exercise will probably be between 8 and 15 minutes depending on your degree of physical conditioning.

You will be given a medical evaluation before entering this study. You will be watched during exercise and a physician will be in attendance. Your heart rate and blood pressure will be recorded during exericse. Your body temperature will be monitored by thermisters (small instruments used to measure temperature) taped to your body, a rectal thermister and a thermister in your ear. You will be breathing into a machine which will analyze oxygen consumption and other changes with exercise.

DoD will provide medical care for DoD eligibles (active duty, dependents, and retired military) for physical injury or illness resulting from participation in this research. Such care may not be available to other research participants. Compensation may be available through judicial avenues to non-active duty research paticipants if they are injured through negligence (fault) of the Government.

If you believe that you have suffered any injury or illness as the result of participating in this research, please contact the Office of Grants Management, 295-3303, at the University. This office can review the matter with you and may be able to identify resources avaialable from the University's Legal Counsel, 295-3028.

Your name will not be used in the publication of this date, nor will your personal data be released without your consent.

You should not donate blood for two weeks after these tests.

STANDARD FORM 93
REV. OCTOBER 1974
GSA FPMR 101-11.8

APPROVED
OFFICE OF MANAGEMENT AND BUDGET No. 29- R0191

REPORT OF MEDICAL HISTORY

(THIS INFORMATION IS FOR OFFICIAL AND MEDICALLY-CONFIDENTIAL USE ONLY AND WILL NOT BE RELEASED TO UNAUTHORIZED PERSONS)

1. LAST NAME—FIRST NAME—MIDDLE NAME		2. SOCIAL SECURITY OR IDENTIFICATION NO.
3. HOME ADDRESS *(No. street or RFD, city or town, State, and ZIP CODE)*		4. POSITION *(title, grade, component)*
5. PURPOSE OF EXAMINATION	6. DATE OF EXAMINATION	7. EXAMINING FACILITY OR EXAMINER, AND ADDRESS *(Include ZIP Code)*

8. STATEMENT OF EXAMINEE'S PRESENT HEALTH AND MEDICATIONS CURRENTLY USED *(Follow by description of past history, if complaint exists)*

9. HAVE YOU EVER *(Please check each item)*

YES	NO	*(Check each item)*
		Lived with anyone who had tuberculosis
		Coughed up blood
		Bled excessively after injury or tooth extraction
		Attempted suicide
		Been a sleepwalker

10. DO YOU *(Please check each item)*

YES	NO	*(Check each item)*
		Wear glasses or contact lenses
		Have vision in both eyes
		Wear a hearing aid
		Stutter or stammer habitually
		Wear a brace or back support

11. HAVE YOU EVER HAD OR HAVE YOU NOW *(Please check at left of each item)*

YES	NO	DON'T KNOW	*(Check each item)*	YES	NO	DON'T KNOW	*(Check each item)*	YES	NO	DON'T KNOW	*(Check each item)*
			Scarlet fever, erysipelas				Cramps in your legs				"Trick" or locked knee
			Rheumatic fever				Frequent indigestion				Foot trouble
			Swollen or painful joints				Stomach, liver, or intestinal trouble				Neuritis
			Frequent or severe headache				Gall bladder trouble or gallstones				Paralysis (include infantile)
			Dizziness or fainting spells				Jaundice or hepatitis				Epilepsy or fits
			Eye trouble				Adverse reaction to serum, drug,				Car, train, sea or air sickness
			Ear, nose, or throat trouble				or medicine				Frequent trouble sleeping
			Hearing loss				Broken bones				Depression or excessive worry
			Chronic or frequent colds				Tumor, growth, cyst, cancer				Loss of memory or amnesia
			Severe tooth or gum trouble				Rupture/hernia				Nervous trouble of any sort
			Sinusitis				Piles or rectal disease				Periods of unconsciousness
			Hay Fever				Frequent or painful urination				
			Head injury				Bed wetting since age 12				
			Skin diseases				Kidney stone or blood in urine				
			Thyroid trouble				Sugar or albumin in urine				
			Tuberculosis				VD—Syphilis, gonorrhea, etc.				
			Asthma				Recent gain or loss of weight				
			Shortness of breath				Arthritis, Rheumatism, or Bursitis				
			Pain or pressure in chest				Bone, joint or other deformity				
			Chronic cough				Lameness				
			Palpitation or pounding heart				Loss of finger or toe	12. FEMALES ONLY: HAVE YOU EVER			
			Heart trouble				Painful or "trick" shoulder or elbow				Been treated for a female disorder
			High or low blood pressure				Recurrent back pain				Had a change in menstrual pattern

13. WHAT IS YOUR USUAL OCCUPATION?

14. ARE YOU *(Check one)*

☐ Right handed ☐ Left handed

Standard Form 88
Revised 10-[illegible]
General Services Administration
Interagency Comm. on Medical Records
FPMR 101-11.806-8

REPORT OF MEDICAL EXAMINATION

1. LAST NAME - FIRST NAME - MIDDLE NAME		2. GRADE AND COMPONENT OR POSITION	3. IDENTIFICATION NO.
4. HOME ADDRESS (*Number, street or R.F.D., city or town, State and ZIP Code*)		5. PURPOSE OF EXAMINATION	6. DATE OF EXAMINATION
7. SEX	8. RACE	9. TOTAL YEARS GOVERNMENT SERVICE: MILITARY / CIVILIAN	10. AGENCY / 11. ORGANIZATION UNIT
12. DATE OF BIRTH	13. PLACE OF BIRTH	14. NAME, RELATIONSHIP, AND ADDRESS OF NEXT OF KIN	
15. EXAMINING FACILITY OR EXAMINER, AND ADDRESS		16. OTHER INFORMATION	
17. RATING OR SPECIALTY		TIME IN THIS CAPACITY (*Total*) / LAST SIX MONTHS	

CLINICAL EVALUATION

NORMAL	(*Check each item in appropriate column, enter "NE" if not evaluated*)	ABNORMAL
	18. HEAD, FACE, NECK, AND SCALP	
	19. NOSE	
	20. SINUSES	
	21. MOUTH AND THROAT	
	22. EARS—GENERAL (*Ext. & ext. canals. Auditory acu. — under items 70 and 71*)	
	23. DRUMS (*Perforation*)	
	24. EYES—GENERAL (*Visual acuity and refraction under items 72, 73, and 74*)	
	25. OPHTHALMOSCOPIC	
	26. PUPILS (*Equality and reaction*)	
	27. OCULAR MOTILITY (*Associated parallel movements, nystagmus*)	
	28. LUNGS AND CHEST (*Include breasts*)	
	29. HEART (*Thrust, size, rhythm, sounds*)	
	30. VASCULAR SYSTEM (*Varicosities, etc.*)	
	31. ABDOMEN AND VISCERA (*Include hernia*)	
	32. ANUS AND RECTUM (*Hemorrhoids, fistulae. Prostate, if indicated*)	
	33. ENDOCRINE SYSTEM	
	34. G-U SYSTEM	
	35. UPPER EXTREMITIES (*Strength, range of motion*)	
	36. FEET	
	37. LOWER EXTREMITIES (*Except feet. Strength, range of motion*)	
	38. SPINE, OTHER MUSCULOSKELETAL	
	39. IDENTIFYING BODY MARKS, SCARS, TATTOOS	
	40. SKIN, LYMPHATICS	
	41. NEUROLOGIC (*Equilibrium tests under item 72*)	
	42. PSYCHIATRIC (*Specify any personality deviation*)	
	43. PELVIC (*Females only. Check how done*) ☐ VAGINAL ☐ RECTAL	

NOTES (*Describe every abnormality in detail. Enter pertinent item number before each comment. Continue in item 73 and use additional sheets if necessary.*)

(*Continue in item 73*)

44. DENTAL (*Place appropriate symbols, shown in examples, above or below number of upper and lower teeth.*)

Restorable teeth; Non-restorable teeth; Missing teeth; Replaced by dentures; Fixed Partial dentures

RIGHT																	LEFT
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17	

REMARKS AND ADDITIONAL DENTAL DEFECTS AND DISEASES

LABORATORY FINDINGS

45. URINALYSIS A. SPECIFIC GRAVITY		46. CHEST X RAY (*Place, date, film number and result*)
B. ALBUMIN	D. MICROSCOPIC	
C. SUGAR		
47. SEROLOGY (*Specify test used and result*)	48. EKG / 49. BLOOD TYPE AND RH FACTOR	50. OTHER TESTS

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